Causes and consequences of hip fracture in men.

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CAUSES AND CONSEQUENCES OF HIP FRACTURE IN MEN

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ABSTRACT

AIMS

The studies in this thesis evaluate the clinical and laboratory risk factors for hip fractures in men with special emphasis on bone mineral density and androgen status and assess its outcome in terms of both its morbidity and mortality.

PATIENTS AND METHODS

100 men aged 50 years and over, living in Cornwall, presenting consecutively with minimal trauma hip fracture were recruited prospectively over 14 months (December 1995-January 1997). 100 age-matched community controls were drawn from a general practice register within the catchment area. Similar data were collected from all cases and controls. Interviewer assisted questionnaires were used to obtain socio-demographic information and assess potential risk factors for fracture, quality of life and concurrent diseases and drugs. Early morning blood and urine samples were collected for biochemical measurements; in the fracture cases they were collected before 9am within 48 hours of admission. All controls and 62 cases had bone mineral density measurements (BMD) at the lumbar spine and proximal femur using dual energy X-ray Absorptiometry (Hologic 1000). In fracture cases measurements were within one week of admission. Both cases and controls were followed-up at 6,12 and 24 months.

RESULTS

Demographic: The mean age of the fracture cases was 80 years (range 54-97) compared to 75 years (range 50-96) in controls. All were Caucasian except for one Chinese. 55 fractures were cervical and 45 intertrochanteric. There was no side predilection; one patient had spontaneous bilateral fracture. Most (67%) fractures occurred indoors.

Co-Morbidity, General Health And Lifestyle: Fracture cases had more co-morbidities, especially previous falls, strokes, impaired vision, restricted mobility, dementia and Parkinson's ($p<0.001$). Mean weight and BMI in fracture cases (67.8kg and 23.4) were significantly lower than in controls (77.7kg and 26.7; $p<0.001$ by t-tests).

Laboratory: Routine laboratory results showed normal acute phase responses following fractures. However, 25-hydroxyvitamin D was significantly lower in fracture cases than controls at the time of the fracture (mean 9.7 ng/ml Vs 18.3ng/ml respectively; $p<0.0001$) and, this difference persisted for 6 months. Vitamin D deficiency was present in 65% cases compared to 14% controls. Total testosterone and free androgen index, though they declined with age in both groups, were significantly lower in fracture cases ($P<0.001$ by t-test) compared with controls initially and remained low at 6 and 12 months. Mean sex-hormone binding globulin, FSH, LH thyroxine, TSH and parathyroid hormone were similar in cases and controls. Hip fracture cases exhibited features of impaired bone turnover (uncoupling): serum osteocalcin was reduced while urinary deoxypyridinoline was raised, compared to controls.

BMD: Cases had significantly lower BMD at all sites compared to controls: lumbar spine ($0.92 g/cm^2$ Vs $1.08 g/cm^2$; $p<0.05$) and the femoral neck ($0.61 g/cm^2$ Vs $0.76 g/cm^2$; $p<0.05$). Using the WHO criteria cases were 7 times more likely to have osteoporosis at the femoral neck and 10 fold more likely to have osteoporosis at the lumbar spine compared to controls.

SF36: Quality of life, assessed by the SF36 at the time of admission, showed a significantly worse pre-morbid health status in the fracture group compared to controls in all domains ($p<0.001$) except pain. This continued on prospective assessment upto 24 months ($p<0.001$).

Mortality: At a mean follow-up of 661 days (1.8 years), mortality was 60% in the hip fracture population against 10% amongst controls. Cause of death was similar in the two groups: chest infections and heart disease being the commonest. Many survivors in the fracture group continued to require institutionalized care 24 months after the fracture.

CONCLUSIONS

The main risk factors for minimal trauma hip fracture in men are low BMD, testosterone deficiency, vitamin D deficiency along with poor general health. Presence of co-morbidities like poor vision, Parkinson's, strokes, poor mobility increase their likelihood for falling and hence fracture. All of these are potentially preventable. The mortality accompanying hip fracture is high; the causes of death are not related to fracture but to poor general ill health. Survivors are left with significant morbidity that requires long-term care.

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Activities of Daily Living (ADL)
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Bodily Pain (BP)
Chi-Square ($\chi 2$)
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C- Reactive Protein (CRP)
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Co-Efficient Of Variation (CV)
Degree Of Freedom (Df)
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European Vertebral Osteoporosis Study (EVOS)
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General Practitioner (GP)
Gonadotrophin Releasing Hormone (GnRH)
Hazards Ratio (HR)
Health Assessment Questionnaires (HAQ)
Health Assessment Score (HAS)
Hip Axis Length (HAL)
Hormone Replacement Therapy (HRT)
Human Chorionic Gonadotrophin (HCG)
Insulin Growth Factor (IGF)
International Units Per Litre (IU/L)
Interleukin (IL)
Luteinising Hormone (LH)
Magnetic Resonance Imaging (MRI)
Mental Component Score (MCS)
Mediterranean Osteoporosis Study (MEDOS)
Mental Health (MH)
Nanogram/Millilitre (Ng/ml)
Nanomol / Nanomol (Nm/Nm)
National Health Service (NHS)
National Health And Nutrition Examination Survey (NHANES)
N-Telopeptide (NTx)
Not Significant (NS)
Number (No)
Odds Ratio (OR)
Osteoarthritis (OA)

Osteocalcin (OC)
Parathyroid Hormone (PTH)
Pearson's Correlation (r)
Physical Component Score (PCS)
Physical Functioning (PF)
Picogram Per Millilitre (pg/ml)
Pyridinoline (Pyr)
Quantitative Computerised Tomography (QCT)
Radio-Immunoassay (RIA)
Recommended Daily Allowance (RDA)
Relative Risk (RR)
Role Emotional (RE)
Role Physical (RP)
Sex Hormone Binding Globulin (SHBG)
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Spearman's Correlation (R_s)
Standard Deviation (SD)
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Total Alkaline Phosphatase (TALP)
Transforming Growth Factor –β (TGFβ)
Urinary Deoxy-Pyridinoline (Udpd)
World Health Organisation (WHO)
25 Hydroxy Vitamin D (25-OH-D)

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Ira Pande *et al* - poster
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1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Historical Perspective

Osteoporosis was first clearly described and the term coined by the Strasbourg pathologist, Jean Georges Lobstein the younger (1777-1835) in the early 1820's (Schapira and Schapira, 1992). It is derived from the Greek words "osteon" (bone) and "poros", (little hole)-literally porous bone. The term was first used as a pathological description and applied to any disorder resulting in a reduction in bone quantity, though it was subsequently distinguished from osteomalacia by Pommer in 1885 (Schapira and Schapira, 1992).

Evidence of age related bone loss or osteoporosis has been found in paleopathological specimens from early antiquity (Perzigian, 1973). One of the earliest representations of clinical osteoporosis, however, is present in pictorial art, in a painting by Vittorio Carpaccio (1465) who, in "the arrival of the English ambassadors' depicts an ageing governess with a dowagers hump and a walking aid (Dequeker, 1994).

In 1842, Astley Cooper noted that fractures might result from an age-related reduction in bone fragility. However detailed study of the relationship between bone fragility and fractures was to wait for over 100 years.

Osteoporosis went unrecognized in almost all English and American textbooks until well into the 20th century – and was then attributed mainly to old age. In middle-aged and younger people it remained unexplained or "idiopathic" until Fuller Albright et al, recognized oestrogen deficiency as its commonest cause in 1940 (Albright *et al*, 1941), and noted a promising response to oestradiol, first isolated only 4 years earlier.

Since then, and particularly during the last two decades, there have been major advances in both our understanding of the pathogenesis, and our ability to measure and quantify osteoporosis as a result of more and more sophisticated methods of investigation and novel forms of treatment. Hip fracture however, remains one of the classic hallmarks of osteoporosis.

1.1.2 Definition and Classification of Osteoporosis

Osteoporosis has been defined as, "...a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (Consensus Development Conference, 1993).

Although widely accepted this definition lacks the detailed classification criteria required to separate individuals into those with and without the disorder. The difficulties arise because the definition is phrased both in terms of a clinical outcome (fracture) and a risk factor (bone fragility), and their relative importance is not specified.

Some advocate classification on the basis of a reduction in bone mass (the major determinant of bone fragility) (Nordin, 1987), however there are difficulties with such an approach as there is no clearly defined threshold value above which fracture risk increases (Cummings *et al*, 1990). Others have suggested restricting classification to individuals who have already sustained an age-related fracture, however such a classification is of limited clinical relevance as it excludes those who are at high risk because of a low bone mass, and in whom preventive measures may be effectively targeted.

A WHO working party recently proposed a classification which incorporates both the notions of reduction in bone mass and fracture (Kanis *et al*, 1994). In this classification, osteoporosis is present when an individual bone mineral content or bone mineral density is less than 2.5 standard deviations below the young normal adult mean value. Such a threshold identifies approximately 30% of postmenopausal women as having osteoporosis- a figure comparable to the lifetime risk of the major osteoporotic fractures at age 50 (Cummings *et al*, 1995; Melton *et al*, 1992). Individuals with evidence of frailty fracture are classified as having severe or established osteoporosis.

The classification includes a separate category (low bone mass) which allows identification of individuals who are at moderately increased risk of fracture, and in whom preventive measures might be considered (about 15% of perimenopausal women, [WHO, 1994]).

Table 1.1 Classification of Osteoporosis (WHO, 1994)

Category	Criteria
I Normal	BMD or BMC not more than 1SD below young adult mean
II Low bone mass (osteopenia)	BMD or BMC between 1-2.5 SD below young adult mean
III Osteoporosis	BMD or BMC >2.5 SD below young adult mean
IV Established osteoporosis (severe)	BMD or BMC >2.5 SD below young adult mean plus one or more fragility fractures

BMD=Bone Mineral Density; BMC=Bone Mineral Content; SD=Standard Deviation

1.1.3 Clinical Manifestation

Low bone mass by itself causes, few, if any symptoms. Except for the possibility of tooth loss (Krall *et al*, 1994) the clinical manifestations of osteoporosis relate exclusively to its associated fractures. It is traditional to link fractures of the proximal femur (hip), vertebrae (spine), and distal forearm (wrist) with osteoporosis; however, because bone is lost throughout the skeleton, almost all types of fractures in the elderly are due in part to low bone density. These include fractures of the distal femur, rib, pelvis, humerus, finger and toe.

Osteoporosis-related fractures can be uncomplicated and followed by full recovery, or they can lead to chronic pain, disability, increased dependence on others for some or all of the activities of daily living (ADLs), deformity to total collapse of the spine, need for nursing home care and death.

The probabilities of the various types of fractures over time have been calculated for an average-risk white women (Cummings *et al*, 1989; Melton *et al*, 1992). For example, the probability that a 50-year-old average-risk white women will have a hip fracture some time in the rest of her life is about 14%. The probabilities are different for African-American women and for men. The lifetime risk of hip fracture has been estimated at 5-6% in white men from age 50 and older (Cummings *et al*, 1989; Melton *et al*, 1992), while lifetime risk for hip fracture for African-American women is about 6% and is 3% for men (Cummings *et al*, 1989). Unfortunately, there is insufficient data on the probabilities of various types of fracture by age for men.

1.1.4 Current Management

Many interventions have been considered for osteoporosis. They range from general public health recommendations-such as diet (calcium), vitamins (vitamin D), exercise, and tobacco cessation- to the use of specific drugs, such as hormone replacement therapy (HRT), calcitonin, fluoride, or one of the bisphosphonates. Some interventions, such as HRT, have multiple effects, while others are specific to osteoporosis.

Contrary to the wealth of information about women, therapy of osteoporotic disorders in men is virtually unexplored and there are no approved pharmacological therapies for osteoporosis in men. There have been very few trials of osteoporosis therapies performed specifically in male populations, although some men with osteoporosis have been included in mixed populations treated with a variety of agents. In general it is very difficult to assess independently the success of these approaches in the male subjects.

Very little information is available on the efficacy of *calcitonin* in men with osteoporosis. In a small randomised study in men with osteoporosis, calcitonin therapy for 2 years produced a decrease in vertebral fracture incidence compared with calcium or multivitamin (Agrawal *et al*, 1981). Men have been included in several trials of calcitonin, but the results in men are not separable from those in women (Burckhardt *et al*, 1993; McDermott and Kidd, 1987). Men have comprised the majority of subjects in some series of patients receiving steroids who responded to calcitonin (Montemurro *et al*, 1991). Although there are few data in men, theoretically calcitonin should be effective in reducing osteoblastic activity in patients with osteoporosis. There have been no trials of any *bisphosphonate* performed exclusively in men. Male patients have been included in mixed patient populations and seem to have a benefit on bone mineral density during treatment with pamidronate (Valkema *et al*, 1989), etidronate (Orme *et al*, 1994) and alendronate (Saag *et al*, 1998). Although specific data are lacking, there is no theoretical reason that bisphosphonates would not be effective in reducing osteoclastic work in men as in women (Papapoulos *et al*, 1992). Slovik *et al* reported that in a small group of men with idiopathic osteoporosis, combined *parathyroid hormone* and 1, 25 dihydroxyvitamin D administration increased spinal bone mass (Slovik *et al*, 1986). Although the role of parathyroid hormone administration in the treatment of osteoporosis remains unclear, its potential appears similar in men and women. As with

previous therapies, there have been no specific trials of *fluoride* administration in men. In some trials, men have been included in the treatment groups (Mamelle *et al*, 1988; Jowsey *et al*, 1972; Riggs *et al*, 1980) but it is difficult to ascertain whether responses were in any way sex-specific.

There have been several reports of small increases in bone mineral density with *androgen replacement* in hypogonadal (Behre *et al*, 1997; Devogelear *et al*, 1992; Diamond *et al*, 1991; Finkelstein *et al*, 1989) and eugonadal men with osteoporosis (Anderson *et al*, 1996). However, there is a lack of studies showing the effect of long-term androgens in men with osteoporosis. In general, the response of BMD to androgen replacement therapy has been modest. Essentially all evaluations of the effectiveness of androgen replacement therapy in hypogonadal men have examined the use of parenteral testosterone or the restoration of endogenous testicular function after treatment of reversible causes. Research still needs to look into the most appropriate route of administration and the specific androgen to be used. The potential risks of androgen replacement, particularly in the elderly, are uncertain in relation to the possible skeletal benefits to be gained. There is essentially no experience with other treatments in therapy of hypogonadal bone loss in men. The character of hypogonadal bone loss in men suggests it is similar to that in women (an early phase of resorption followed by lower turnover), so approaches that have been effective in postmenopausal women (bisphosphonates, calcitonin) may be useful in men. Treatment of osteoporosis in men remains unclear as there is a lack of randomised controlled studies with fracture as the end point assessing the different options. The UK Consensus Group for the management of male osteoporosis recommended the use of bisphosphonates and the consideration of sodium fluoride and anabolic steroids in the case of treatment failure (Eastell *et al*, 1998).

In conclusion, despite the wealth of information on women there is dearth of data on lifetime risk of osteoporotic fractures and their management in men. Future studies are needed exclusively addressing these issues in men.

1.2 EPIDEMIOLOGY OF HIP FRACTURES

1.2.1 Introduction

Fracture is the clinical manifestation of osteoporosis that leads to its health, social and economic impact. Our knowledge of the occurrence of fractures is an important starting point in assessing the social and economic impact of osteoporosis. Of all osteoporotic fractures, hip fracture is the commonest and the major cause of mortality and disability in the elderly. With increasing numbers of elderly people, the burden on health care will become a critical issue for public health in many developed and developing countries. However, there is remarkable variability in the incident rates of hip fracture in various geographic regions. The epidemiology of hip fractures has been extensively studied in women using available data from countries and projections made for the future. However, data on men is scarce.

1.2.2 Incident rates for hip fracture world-wide

The incident rates for hip fracture in men and women aged 50 years and over in different countries throughout the world over a 30 years period (between 1960 –1990) have been reviewed by Maggi *et al* (1991). Incidence rates increased with age over the 30-year period in all geographic areas and ethnic groups, in both sexes. A significant difference in incidence was seen between sexes and age groups in all countries studied. The highest annual incidence of hip fracture was seen in Norway, Sweden, Denmark, New Zealand and US (>350/100,000); intermediate rates (150-349/100,000) in the UK and Finland and lower rates (149/100,000 or less) in Singapore and Hong Kong. There is dearth of data from Asian countries, which failed to derive any conclusions. Possible explanations to account for these differences in incident rates were the degree of industrialisation and hours of sunlight exposure.

The comparisons made in the above study were based on incidence of hip fracture from limited geographic regions within a country. The same group (Bacon *et al*), in 1996 re-addressed this issue looking at national hospital discharge data for a specified time interval (1988-89) in nine countries (Canada, Chile, Finland, Hong Kong, Scotland, Sweden, Switzerland, USA and Venezuela) using more stringent criteria. Due to potential problems in definition of "discharge", data from each country was compared to US data that had been

adjusted to account for differences. From each country number of patients with a diagnosis of femoral neck fracture based on the International Classification of Diseases, Ninth Revision code 820 was obtained. Simultaneously, population by sex and age groups for 1988 and 1989 were obtained. The groups were 50-59 years, 5 year age groups from 60-84 years, and 85 years and older. To minimise multiple counting of the same fracture case, countries were asked to send data excluding transfers from or to other hospitals. This study confirmed the previous findings that hip fracture rates increased with age and varied across nations. However, hip fracture rates in north European and North American countries appeared to be more similar than previously thought.

The Mediterranean Osteoporosis Study (MEDOS) group (Johnell *et al*, 1992) in collaboration with the WHO and the European Foundation for Osteoporosis addressed the incidence of hip fractures in 17 European countries (representing 46% of the European population with a potential catchment of 83 million). The group looked at number of hip fractures by age and sex between the years 1983-1985. Population data if not obtained from the country concerned was obtained from the United Nations demographic yearbook. Incidence rates were standardised to the population of Sweden using 10-year intervals. In seven countries 100% of the known cases of hip fracture were obtained, whereas in others it was an estimate based on a sample ranging from 10-85% of the population. In some countries data was available only from selected geographic areas.

Their data also confirmed the marked differences in the incidence of hip fracture between sexes, by age and by country of origin. Also, an increase in incidence with age in both sexes and in all countries was noted. However, larger differences in incidence between countries were reported with 11-fold variation amongst women and 7 fold amongst men. Like previous researchers, the highest incidence was found in the northern Europe, slightly less in Central Europe, with the exception of Poland, and low in southern European countries. The incidence rate for hip fracture in men aged 50 years and over in England was interpolated as 114 per 100, 000 with a sex ratio of 2.9.

A more recent cross-national study of hip fracture incident rates was carried out in five geographical areas- China, Hungary, Hong Kong, Brazil and Iceland over a 2 year period (Schwartz *et al*, 1999). Cases were identified using hospital discharge data. Estimated

incidence rates varied widely, with Beijing reporting the lowest and Iceland the highest. Similar to previous reports, this study concluded that the differences amongst countries reflect genuine variation in hip fracture incident rates.

The only prospective-population based study aimed at defining incidence of hip fractures in different countries using same sampling techniques in contrast to previous studies based on national registers was the second part of the MEDOS study (Elffors *et al*, 1994). Hip fractures were recorded prospectively in defined catchment areas over a 1-year interval (1988-89) in 6 southern European countries (14 European centres). A total of 3629 men and women over the age of 50 years with a hip fracture were identified from a catchment of 3 million. In all communities fracture rate increased exponentially with age. Lowest rates were observed in Turkey and the highest in Spain and Portugal. There were large and significant differences between centres in the doubling time of hip fracture risk with age and in crude and age-standardised rates. Similar to the conclusion of the first part of the study, the authors showed marked and sizeable differences in incidence rates of hip fracture amongst Mediterranean European countries and related them to lifestyle and genetic differences.

1.2.3 Influence of Age, Sex, and Ethnicity

All studies stated earlier (Maggi *et al*, 1991; Bacon *et al*, 1996; Johnell *et al*, 1992; Elffors *et al*, 1994; Schwartz *et al* 1999) have consistently shown that majority of hip fractures in any country occur in the elderly and that the incidence increases with age and in both sexes in all countries where data is available. The proportion of hip fractures found in women over age 80 years ranged between 37-66% (Johnell *et al*, 1992) across all countries, with the exception of Turkey and Yugoslavia where only one quarter of fractures were aged 80 and older.

Most studies have found an exponential rise in the incidence of hip fractures with age, particularly after the age of 45 years. The exponential rise was more marked in women, so that the female to male ratio for the MEDOS study rose from 1.1 between age 50-54 years to >2.0 over age 70 years (Elffors *et al*, 1994). On similar lines, using the regression model on the prospective data collected from southern Europe (Johnell *et al*, 1992) researchers

calculated the doubling time of hip fracture between 5-7 years in women and 6-10 years in men. However, significant differences were noted in doubling time amongst females, males and also between sexes in each country studied. In Europe, the highest doubling time was in Yugoslavia, the lowest in Iceland and Malta (Johnell *et al,* 1992).

The MEDOS study has also shown a significant positive correlation (r=0.85) between life expectancy and risk of hip fracture. Highest rates were observed in Sweden and Iceland where life expectancy at age 70 years is among the highest in the continent (over 14 years) (Johnell *et al,* 1992).

There was a marked difference in the incidence of hip fracture between sexes by age and country of origin within the European countries (Johnell *et al* 1992; Elffors *et al*, 1994). The number of hip fractures were significantly greater amongst women than men except in Turkey and Yugoslavia where it was equally common (Johnell *et al*, 1992) and in China where rates for men were higher (Schwartz *et al*, 1999). There was a 3-fold range between countries in the female to male sex ratio; varying from 1.3 (Yugoslavia) to 4.2 (Iceland) see Table 1.2. There was an 11-fold range in the apparent incidence among women and a 7-fold range amongst men between countries (Johnell *et al*, 1992). However, this variation in incidence between sexes was less than differences between regions. There was a significant positive correlation between age-standardised incidence rates reported in men from each country and that in women.

The risk of having a fracture at the age of 80 is significantly greater in women than in men and ranges between 3% to 19%. In the MEDOS study the risk of hip fracture at age 80 years in England was 7% for females and 3% for males (Johnell *et al,* 1992). In contrast the figures for Sweden were 19% and 13% and for Malta 3% and 2% respectively.

Age and sex-adjusted hip fracture rates are generally higher in Caucasians than in Asian and Black populations (Maggi *et al,* 1991; Bacon *et al,* 1996). The female to male ratio is greater than 1 in the white population with the exception of Chilean and Finnish males aged 50-59 years (Maggi *et al,* 1991; Bacon *et al,* 1996). The rates were higher in females than males in Hispanics also. However, the number of cases studied were not enough. The ratio is reversed for blacks, Asians (Maggi *et al,* 1991; Bacon *et al,* 1996) and Chinese (Schwartz

et al, 1999). However, more recent surveys from Asians and blacks living in the west have shown that the male to female ratio is similar to those in the white population with rates higher in women than in men. These differences in sex ratio between studies carried out in the developing world versus those in the West seems to further support an effect of environmental factors in the aetiology of hip fractures. The more recent study by Gullberg and colleagues (Gullberg *et al*, 1997) also showed a good correlation between sexes within a community.

1.2.4 Burden of hip fractures in men compared to women

There were an estimated 1.66 million hip fractures worldwide in 1990. According to epidemiological projections, the total number will rise to 3.94 million (1.16M men) in 2025 and 6.26 million (1.79M men) by 2050. This rise will be in great part due to the huge increase in the elderly population of the world. In 1990, 28% of these hip fractures occurred in men (Cooper *et al*, 1992). All over the world the age-adjusted and age-specific hip fracture incidences were about two times higher in women than in men (Kanis 1993; Melton 1993).

The lifetime risk of hip fracture is 5-6% in white men, 2.8% in black men, 16-18% in white women and 6% in black women (Cummings *et al*, 1989). A recent life time risk estimate taking into account the projected life expectancy in the male population, came to slightly higher estimates: 11.1% in men versus 22.7% in women at age 50 years; 10.1% in men versus 20% in women at age 80 years (Oden *et al*, 1998). Lower age-specific incidence and shorter life expectancy in men explain the difference in lifetime risk. Hip fracture incidence in men reaches the same level as in women, at an about 5-6 year older age. For example, 80 year old males have the same hip fracture risk as 75 year old females (De Leat 1997).

The incidence of hip fracture in many Western countries has increased considerably over the past 30 years. This is due to an increase in age-specific rates as well as an increase in age of the population. In the UK, Boyce and Vessey compared the incidence of hip fracture in Oxford in 1954-58 and in 1983 (Boyce and Vessey, 1985). They found that over this 28-year period the age-specific incidence had doubled in both men and women. However, studies looking at secular trends have reported the increase in age-adjusted hip fracture

incidence to be greater in men (80%) than in women (51%) (Parkkari *et al*, 1994). The recent study in Wessex showed a rise in the annual mean number of hip fractures from 330 men and 1496 women in 1978-81 to 568.5 men and 2405.5 women in 1993-5 (McColl *et al*, 1998). This represented an overall increase of 18.8% for men and 15.2% increase for women.

The importance of hip fracture in the UK was reviewed by the Royal College of Physicians in 1989 (Hoffenberg *et al*, 1989). The report concluded that in England, hip fracture patients occupy one-fifth of all orthopaedic beds and the direct hospital costs were estimated at 160 million pound per year using 1987/8 prices. More recent estimates suggested the cost at £198 million per year (Kanis, 1993). Hip fractures have an overall mortality of 15-30% (Browner *et al*, 1996) with one year mortality following hip fracture of around 30% in men and 20% in women (Johnell *et al*, 1993). The excess mortality is of a smaller magnitude and shorter duration among women compared to men (Melton *et al*, 1998). Compared to similar populations of the same age and sex without fracture the excess mortality is 12-20% (Miller, 1978). This excess mortality is mainly in the first year after fracture. Hip fractures are also associated with considerable morbidity, necessitating hospital admissions for an average of 20-30 days (Johnell *et al*, 1992). There have been reports of higher rates of hospitalisation and institutionalisation following fracture in men compared to women (Reginster *et al*, 1999).

Table 1.2 Studies of incidence rates of hip fracture: men versus women

Country	Race	Year of study	Men	Women	Men:Women	Source	Reference
Norway	White	1978-79	301	701	22:102	All hospitals	Falch *et al*
	White	1983-84	551	1293	281:728	Hospital records	Finsen & Benum
Sweden	White	1972-81	291	622	2929:8883	Inpatient care register	Hedlund *et al*
Finland	White	1968	249*	100	417:1025	National Board of Health Statistics	Alhava *et al*
Iceland		1990-92	349	697	Total 579	Hospital discharge data	Schwartz *et al*
Denmark	White	1973-79	203	620	783;2313	Hospital discharge data	Frandsen *et al*
Budapest		1990-92	251	316	Total 407	Hospital discharge data	Schwartz *et al*
UK	White	1973-77	96	275	2469:7800	Hospital activity analysis	Baker *et al*
USA	White	1965-74	174	510	87:328	Diagnostic index-Mayo clinic	Gallagher *et al*
	White	1980	205	530	Total 1346	17 hospitals	Bauer *et al*
	White	1983-84	207	559	10,000:30,000	California Discharge data	Silverman *et al*
	Black	1983-84	144	219			Silverman *et al*
	Asian	1983-84	104	338			Silverman *et al*
	Hispanics	1983-84	90	197			Silverman *et al*
	Hispanics	1980	118	263	Total 1346	17 hospitals	Bauer *et al*
Brazil		1990-92	170	327	Total 472	Hospital discharge data	Schwartz *et al*
Johannesburg	Black	1950-64	38*	26	48:30	Medical records of all hospitals	Solomon *et al*
Hong Kong	Asian	1965-67	96	153	386:654	95% of all fractures	Chalmers *et al*
	Asian	1985	181	353	275:605	Hospital admissions records	Lau *et al*
		1999-92	270	428	Total 3266	Hospital discharge data	Schwartz *et al*
New Zealand	White	1973-76	182*	107	1166:3480	National Health Statistics Centre	Stott *et al*
Singapore	Asian	1955-62	100*	75	402:240	One hospital	Wong *et al*
Beijing		1990-92	107*	96	Total 5881	Hospital discharge data	Schwartz *et al*

Incident rates are age adjusted (per 100,000) of hip fracture by sex in the population over 50 years of age, by geographic area

1.2.5 Future Projections

In 1990, Cooper *et al* used epidemiological literature on hip fracture incidence in various regions of the world and demographic projections obtained from the US Bureau of the Census International Database to estimate the number of hip fractures in different parts of the world. They used this data to make future projections for the years 2025 and 2050. In 1990, there were 1.66 million hip fractures over the world among people aged 35 years and over; with Europe and N America accounting for about half of all hip fractures. The authors projected an increase to 3.94 million (1.16 million men and 6.26 million women) by the year 2025 and 6.26 million (1.79 M men and 4.47 M women) by the year 2050. Their data clearly showed that as a result of these demographic changes there will be a dramatic increase in proportion of all hip fractures in Asia and Latin America with corresponding reduction to around a quarter in Europe and N America. The increase in men would be far greater than the increase in women.

A more recent study (Gullberg *et al* 1997) projected figures along similar lines. According to the authors, in the year 2025 the number of hip fractures will be 2.6 million with 30% in men assuming no change in age-and sex- specific incidence worldwide. The figures would be 3.6 million assuming a conservative 1% increase. A 1% increase in fracture rate per year predicts a further 42% increase in frequency in 2025 and 82% increase in 2050. This is an increase of 135% in men and 100% in women. The more marked increase in men was attributed to improving life expectancy.

Clearly, both studies helped characterise the health burden posed by hip fractures on a global scale. They emphasised that hip fractures represent a global problem, rather than a regional issue and warrant a degree of urgency on international health care agenda. Preventative strategies will have to be tailored to the needs and resources of the region.

1.2.6 Conclusion

With the constraints of imperfect data capture, all studies conclude that there are marked differences in the incidence of hip fracture by age, country of origin and gender. Although

hip fracture is well recognised to be more frequent in women than men, it is of particular interest that the range in sex ratio between countries was less than the range in incidence rates within each sex from the various communities. Although, no conclusions regarding aetiology of hip fractures can be made from this, most authors have suggested differences in genetic and environmental factors of greater importance than differences between sexes. If true, identification of these may be relevant for future prevention. Despite the marked differences it is clear that hip fracture is common and represents a major health care problem in all countries.

The frequency of hip fracture appears to be increasing in many countries. The reason for this is two folds. Firstly, life expectancy over the age of 50 years has increased and will continue to do so. This means progressively more of the population will be elderly, and at risk of fracture. Secondly, there appears to be an increase in age-and sex-specific rates in many countries that will affect future projections. Estimates of lifetime risks of hip fracture appear to vary markedly from country to country and even within countries. Within Europe the range is approximately 11 fold but may be higher throughout the world. Currently, the risk is lower in the developing countries but there is evidence that the incidence is rising and approaching figures in the Western countries. Projections based on population figures clearly show that the proportion of cases with hip fracture will steeply increase in Asia suggesting that osteoporosis will truly become a global problem in the not too distant future. Reasons for the apparent differences in incidence between countries are conjectural. They may be artefacts due to non-standardized methods of data capture or a reflection of genetic and environmental factors. Comprehensive studies with special emphasis on the burden of osteoporosis in men need to be performed.

1.3 RISK FACTORS (NON BMD) FOR OSTEOPOROTIC HIP FRACTURE

1.3.1 Background

Low bone mass is an most important risk factor for hip fracture. However, there have recently been several large, well-conducted studies examining the risk of having a hip fracture independent of low bone mineral density. These factors probably operate through the effects on the risk of trauma and or on skeletal strength.

The following section summarises the methodologies used by the various investigators. There have been two case-control (Poor *et al*, 1995; Grisso *et al*, 1997) and a number of prospective studies focusing on either one (Kiel *et al*, 1996; Langlois *et al*, 1998) or multiple risk factors (Hemenway *et al*, 1994; Nguyen *et al*, 1996; Mussolino *et al*, 1998).

Poor used a population-based nested case-control study design and addressed the role of a number of risk factors for hip fracture exclusively in men. His cohort comprised of 232 men aged more than 35 years with a moderate trauma hip fracture and an equal number of aged matched controls from the general population. Data on potential risk factors was obtained from medical records. The Hip Fracture Study Group (Grisso *et al*, 1997) also used a case-control study design and enrolled 356 men aged 45 years and older with first hip fracture between 1991-93 along with 402 community controls. Information on potential risk factors was obtained through personal interviews at a median duration of 6.5 weeks from hip fracture occurrence.

A longitudinal epidemiological study assessed risk factors in 820 elderly men (aged 60 years or more) in the city of Dubbo, Australia (Nguyen *et a,* 1996*)*. Subjects were followed for over 5 years during which 31 men with hip fractures were identified. Similar prospective population-based study design was used by Mussolino *et al* to assess predictors of hip fracture risk in men participating in the NHANES survey. The authors identified a cohort of 2879 men aged 45-74 years at entry (1971-75) and identified 71 hip fractures over a 22-year period. Another prospective study (Hemenway *et al*, 1994) examined risk factors in approximately 50,000 health professionals (49,895 men) who were between the ages of 40 and 75 years in 1986 and identified 67 hip fractures by 1992.

Most of the above mentioned studies addressed the role of anthropometry (height,

weight, body mass index), lifestyle factors such as activity, smoking, alcohol, co-morbid diseases and medications as risk factors for hip fracture exclusively in men. The Framingham study (Kiel *et al*, 1996) exclusively addressed the issue of smoking at different life stages on BMD. They used a population - based cohort study design and collected data prospectively over a 40-year period. Similarly, the more recent cohort study by Langlois (Langlois *et al*, 1998) exclusively investigated the effects of change in body weight on risk of hip fracture. The workers used data from the Established Populations for Epidemiologic Studies of the Elderly (EPESE) comprising a cohort of 2413 men who were followed for over 8 years during which time 72 hip fractures were noted. Change in body weight from age 50 years to old age was recorded and its role as risk factor for hip fracture was analysed.

From the above it is quite clear that compared to the extensive literature available for women, data in men are limited in the number of hip fractures studied. The following section aims to draw useful conclusions from the evidence that exists in literature on the role of various factors other than BMD that influence the risk of hip fracture in men.

1.3.2 Genetic contribution

Maternal history of osteoporosis and or fracture is a well-recognised risk factor for osteoporosis in women. There is dearth of literature for men. The Rancho Bernado Study (Soroko *et al*, 1994) looked at the association between family history of osteoporosis and BMD in a cohort of 1477 white elderly non-institutionalised ambulatory subjects that included 600 men. Their study showed a significant relationship between maternal history of osteoporosis and lower BMD at the hip in men.

A recent study has confirmed that polymorphism of an Sp1 binding site of the Col1a1 gene is significantly associated with osteoporotic vertebral fracture in men and the effect on fracture risk is partly independent of BMD (Langdahl *et al*, 1998). There is no study to date addressing the role of any candidate genes as risk factors for hip fracture in men.

1.3.3 Anthropometry: height, weight and body mass index

The relationship of *height* to risk of fracture has been studied by a number of workers (Meyer *et al*, 1993 & 1995; Hemenway *et al*, 1994; Poor *et al*, 1995; Nguyen *et al*, 1996; Grisso *et al*, 1997). Most studies have suggested taller height to be an independent risk factor for hip fracture (Meyer *et al*, 1993; Hemenway *et al*, 1994; Poor *et al*, 1995)

with an odds ratio of 1.6 per 6 cm increase in height (Grisso *et al*, 1997). One possible explanation for this is the strong association of height with hip axis length, itself a risk factor for hip fracture. In contrast, Nguyen and co-workers (Nguyen *et al*, 1996) found men with both hip and vertebral fractures to be about 6 cm shorter than non-fracture controls. After adjusting for femoral neck BMD, shorter (current) height was a significant risk factor for fracture. Since height decreases with advancing age it has been suggested that measurement of current height may not be as reliable as peak height in assessing the fracture risk of an individual.

The relationship between *weight* and risk of hip fracture has been studied using "current weight", "weight gain" and "weight loss" over defined periods and linking these to risk of hip fracture. All studies confirm low weight to be a risk factor (Nguyen *et al*, 1996; Langlois *et al*, 1998; Mussolino *et al*, 1998). The longitudinal study by Nguyen and co-workers in Dubbo, Australia involving 820 men aged over 60 years showed higher weight was protective against fracture risk but was not independent of BMD (Nguyen *et al*, 1996). The more recent Established Populations for Epidemiologic Studies of the Elderly (Langlois *et al*, 1998) assessed the risk of hip fracture associated with weight change between middle (50 years) and old age in men. The study confirmed extreme weight loss (>=10%) beginning at age 50 associated with a near 2-fold increased risk of hip fracture (RR 1.8). Similarly, weight gain of 10% or more provided borderline protection (RR 0.4). Similar results were obtained from another prospective study even after adjustments were made for the presence of co-morbid conditions (Mussolino *et al*, 1998). A weight loss of 10% or more from maximum was associated with a two fold risk of hip fracture (OR=2.31). One limitation of this study was the very small number of hip fractures (n=71). However, on comparison of those with BMI less than to more or equal to 25.7, amongst those who lost 10% or more weight; fracture risk was higher in the "thinner" than "heavier" men (Mussolino *et al*, 1998).

Although low *BMI* is a significant predictor of hip fracture risk in women it has not been consistently related to hip fracture risk in men. One possible explanation comes from the Framingham data (Felson *et al*, 1993) which suggests that body weight has less influence on BMD in men than in women and that past body weight is not as strongly related to bone density as current weight. Thus relationship between BMI and hip fracture risk might be more difficult to detect when based on measurements made many years prior to the fracture. Body weight was related to hip fracture risk in men based on

measurements made within 6 weeks to 5 years of duration but BMI did not differ between men with and without hip fracture in a study with 14 years follow-up (Mussolino *et al*, 1998). Similarly, no relationship was found between BMI and risk of hip fracture in 51,529 male health professionals in the US aged 40 through 75 years (Hemenway *et al*, 1994). On the contrary, in a case control study using current anthropometric measurements (Grisso *et al*, 1997) men in the lowest quintile of body mass were at increased risk of hip fracture compared with men in the heaviest quintile (OR 3.8). Similarly, low BMI was confirmed to be a risk factor for hip fracture in middle -aged Norwegian men (Meyer *et al*, 1993) and older white men (Langlois *et al*, 1998). Both these were longitudinal studies of 12 and 8 years duration respectively. Baseline BMI had a strong and statistically significant trend of decreasing rate of bone loss with increasing BMI over a 2 year period in the Rotterdam study (Burger *et al*, 1998).

1.3.4 Hip axis length

Recent studies have suggested that geometric characteristics of the proximal femur may be additional important determinants of fracture risk (Faulkner *et al*, 1993; Boonen *et al*, 1995; Peacock *et al*, 1995; Karlsson *et al*, 1996). In women, an increase in hip axis length (the linear distance from the base of the greater trochanter to the inner pelvic rim along the line through the mid point of the femoral neck) has been linked with hip fracture risk in several studies (Faulkner *et al*, 1993; Duboeuf *et al*, 1997). A one standard deviation increase in hip axis length (HAL) is associated with a 1.8 fold increase in hip fracture risk (Faulkner *et al*, 1993) with the effect being independent of bone mass. There are, however, no data concerning the influence of HAL on risk of hip fracture in men. Two previous studies suggested no difference in femoral neck axis length (one of the component parameters of HAL) among fracture cases than controls Peacock *et al*, 1995), however, the link between FNAL and hip fracture risk is less clear (Karlsson *et al*, 1996; Center *et al*, 1998).

The mechanism by which an increase in HAL confers an increase in susceptibility to fracture in women is unknown. Studies suggest that the risk persists after adjustment for body height and weight indicating it is not a surrogate for body size (itself linked with an increased risk of hip fracture) (Faulkner *et al*, 1993). It has been suggested that HAL is a marker for the ability of the femur or pelvis to absorb or avoid the impact of a fall (Faulkner *et al*, 1995). There are important gender differences in both the shape of the

proximal femur and pelvis including the pelvic brim (Beck *et al*, 1992; Wahner *et al*, 1994) which may influence bone strength or resistance to fracture. In females, the acetabular diameter is usually less than that in males, not only because it is absolutely smaller but also because the anterolateral wall of the cavity is comparatively and absolutely wider. It is possible that one or more of these shape parameters interact with a long hip axis length to increase susceptibility to hip fracture, and explain the discordance in fracture risk in men and women.

1.3.5 Previous history of a fracture at any site

Most but not all studies confirm past history of fracture as risk factor for future fractures. Using a case control study design, history of fracture within 5 years significantly increased fracture risk among elderly men (Nguyen *et al*, 1996). This was true even after adjusting for BMD at the femoral neck. Similar findings were reported using case control (Poor *et al*, 1995), longitudinal (Hannan *et al*, 1992) and observational study designs (Jonsson *et al*, 1993). Results of the NHANES Epidemiological study (Mussolino *et al*, 1998) on the contrary did not support this observation. These differences may be a explained on the way previous fracture was defined "5 years" versus "anytime" increasing the likelihood of the former to be related to osteoporosis and hence significant.

1.3.6 Age

Increasing age has been found to be a risk factor for hip fracture in a number of studies (Hemenway *et al*, 1994; Nguyen *et al*, 1996; Langlois *et al*, 1998; Mussolino *et al*, 1998). A population based prospective study of middle aged adults in 3 Norwegian counties (including 27,015 men) over a 12 year period showed that age is a significant risk factor for hip fracture with a relative risk of 1.67 for every 5 year increase in age (Meyer *et al*, 1993. This is supported by the findings of the longitudinal population based study in Rotterdam that assessed the effect of age on rate of bone loss over a median 1.8 year period (Burger *et al*, 1998). The study showed statistically significant acceleration of bone loss with increasing age up-to 80 years, most clearly in men.

1.3.7 Smoking

The effect of smoking is less clear. Most studies that have looked at the relationship between smoking, risk of hip fracture and BMD have confirmed an increased risk of hip

fracture along with lower BMD in smokers (Meyer *et al*, 1993; May *et al*, 1994; Egger *et al*, 1996; Grisso *et al*, 1997; Mussolino *et al*, 1998). However, in case controls studies (Grisso *et al*, 1991; Poor *et al*, 1995) and in the prospective study of 50,000 male health professionals in the US (Hemenway *et al*, 1994) no significant relationship was observed between smoking and risk of hip fracture. The latter may be a biased sample of healthy individuals. In the Leisure World Study (Paganini-Hill *et al*, 1991) current cigarette smoking increased hip fracture risk in men (OR 2.2) compared with never-smoking, but the risk for past smokers was not different from that of lifetime non-smokers. The association between smoking and hip fracture may partly reflect the lower body weight of smokers. After allowing for body weight, the association persisted in most studies but not in some. Both current and past smoking, including pipes but not cigars increased the risk of hip fracture (OR range 1.4-3.2) independent of body mass and no reduction in risk was detected with increased duration of quitting (Grisso *et al*, 1997). Results of prospective studies (Nguyen *et al*, 1996; Mussolino *et al*, 1998) again suggested an increased risk of fracture amongst current smokers although the risk did not reach statistical significance. Excess smoking (equal or more than 15 cigarettes/day) was found to be a risk factor in the prospective study involving middle aged Norwegians (Meyer *et al*, 1993). In the Rotterdam study (Burger *et al*, 1998) cigarette smoking was accompanied by a substantially higher rate of bone loss at the femur in both men and women. The Framingham Study exclusively addressed the effect of smoking at different life stages on BMD in elderly men (Kiel *et al*, 1996). The study showed smoking at all stages to have an adverse effect on the skeleton. This was independent of weight, alcohol or caffeine use, implying other mechanisms for its effect on bone. A recent meta-analysis of cigarette smoking, BMD and risk of hip fracture (Law and Hackshaw, 1997) suggested a similar effect on BMD and risk of hip fractures in the two sexes. The authors concluded that the data for smoking in men is limited and the variation in mean age between studies is too narrow to permit regression analysis on age.

1.3.8 Alcohol

Results for alcohol have been varied somewhat in previous prospective studies in men. Moderate alcohol consumption has been suggested to be associated with an increase in BMD (Holbrook *et al*, 1993; Glynn *et al*, 1995). Nevertheless, alcohol abuse is associated with osteoporosis, and in particular with an increased fracture risk (Saville 1965; Seeman *et al*, 1983; Felson *et al*, 1988; Slemenda *et al*, 1992). Nguyen *et al* found

a decrease in rate of bone loss over a 2-year period in self reported alcohol drinkers but found no relationship to fracture risk after adjusting for bone density (Nguyen *et al*, 1996). Similarly, no relationship between hip fracture risk and alcohol use was noted in a longitudinal study of 2879 men followed for 22 years (Mussolino *et al*, 1998). The two case-control studies similarly did not find an association between current or past alcohol intake and risk of fracture despite a relatively high prevalence of heavy use (Grisso *et al*, 1991; Poor *et al*, 1995). Similarly, in the Rotterdam study no convincing relationship between alcohol consumption and bone loss at the proximal femur over 2 years was noted (Burger *et al*, 1998). On the contrary, a variable relationship with heavy alcohol usage according to age group was found in the Framingham cohort. Heavy current alcohol consumption was associated with a modestly increased risk of hip fracture for men (RR=1.3) after adjusting for age (Felson *et al*, 1988). Differing results for alcohol use may be due to differences in the way in which these variables are measured.

1.3.9 Calcium

A recent meta-analysis of prospective studies in women concluded that increased calcium intake is associated with a small reduction in fracture risk (Cummings *et al*, 1997). Results from prospective studies on hip fracture that have included men have been mixed. The NHANES epidemiological follow-up study (Mussolino *et al*, 1998) over 22 years addressing this issue in men showed that although not statistically significant, men with higher calcium (and protein) intakes had lower risk of hip fracture even after adjusting for energy intake. Similarly, in the Rotterdam study (Burger *et al*, 1998) a significant trend of lower rates of bone loss with increasing dietary calcium intake was demonstrated. A more recent publication by the Dubbo Epidemiology Study group showed a positive correlation between dietary calcium intake and BMD at both the lumbar spine and proximal femur in men (Nguyen *et al*, 2000). By contrast, there have been reports showing no correlation between dietary calcium intake and BMD in men (Glynn *et al*, 1995).

1.3.10 Exercise and activity

The role of life-style factors as determinants of BMD and hence fracture risk has received considerable attention. Higher physical activity has been shown to be protective against fracture risk (Cooper *et al*, 1988; Lau *et al*, 1988; Mussolino *et al*, 1998; Nguyen *et al*, 1996) with odds ratio of 0.2 for activities equal to or more than 7 hours

per week (Grisso *et al*, 1997). The Leisure World Study similarly showed a strong and negative association between active exercise and hip fracture risk with an odds ratio of 0.5 in men for 1 or more hours of exercise per day compared with less than half hour of exercise (Paganini-Hill *et al*, 1991). The degree of protection conferred has been shown to be irrespective of type of activity (Grisso *et al*, 1997). Similarly, lower limb dysfunction and use of ambulatory aids (Grisso *et al*, 1997) has been shown to be associated with an increased risk of hip fracture. The Rotterdam study (Burger *et al*, 1998) similarly demonstrated higher rates of bone loss with lower limb disability, probably through its association with reduced physical activity. In addition the presence of upper limb dysfunction and difficulty with one or more instrumental activities of daily living has also been shown to be associated with increased risk of fracture (Grisso *et al*, 1997).

1.3.11 Medications

Few studies have addressed specifically the correlation between medicinal intake and hip fracture risk in men. There is lack of consistency in the drugs implicated. Despite the rather common use of diuretics (22% of controls) no significant association was been found between the use of thiazides diuretics and hip fracture risk (Poor *et al*, 1995; Grisso *et al*, 1997; Langlois *et al*, 1998). In contrast, use of psychotropic drugs were shown to double the risk of hip fracture (Grisso *et al*, 1997). Similar strong associations have been reported between risk of fracture and cimetidine use (Grisso *et al*, 1997). Using a case-control study design, Poor and colleagues did not demonstrate a deleterious effect of corticosteroids and anticonvulsants on hip fractures in men (Poor *et al*, 1995). In contrast, using the same study design oral steroids and anticonvulsants were both associated with a significantly increased risk of vertebral fracture in men (OR 6.1) (Scane *et al*, 1999)

1.3.12 Co-morbid diseases

Almost all studies confirm the presence of co-morbid diseases as risk factors for hip fracture (Mussolino *et al*, 1998). Using a case-control study design Poor and colleagues demonstrated significantly increased risk of hip fracture in association with hemiplegia (OR 2.6), Parkinson's (OR 8.0), dementia (OR 5.3), blindness (OR 5.5), vertigo (OR 6.0) or anaemia around the time of fracture (OR 2.6) (Poor *et al*, 1995). More prominent risk factors included a history of thyroidectomy (OR 5.0), gastric resection

(OR 2.6), pernicious anaemia (OR 3.8) and chronic bronchitis (OR 2.3). Similar results were obtained in another case-control study (Grisso *et al*, 1997). The authors demonstrated specific chronic illnesses (stroke, Parkinson's disease) as well as having two or more chronic illnesses to be associated with increased risk of fracture. An explanation for the association is the probable link between these disorders and secondary causes of osteoporosis or an increased likelihood of falling.

1.3.13 Synopsis

Many risk factors for fractures are comparable between the sexes, such as low body mass index, inactivity, low diet calcium, excess alcohol intake, heavy smoking and presence of co-morbid condition. Risk factor analysis may be helpful in designing strategies for preventing hip fractures. Some risk factors act at least partly through effects on bone density, whereas others act by influencing the risks of falls. Many of these factors can be eliminated or modified. Even those that cannot be modified are important for identifying at-risk patients, who may benefit most from therapies that alter other risk factors. However, risk factor assessments are not a substitute for BMD measurements and cannot be recommended as screening tools in their own right due to variable results. They may however, provide valuable information to a BMD scan, particularly for risk of falls. Knowledge of risk factors may also contribute to the clinical treatment of individual patients. Information about risk factors helps in the understanding of disease causation. Clearly, large prospective studies encompassing all risk factors are warranted in men.

1.4 BONE MINERAL DENSITY AS RISK FACTOR FOR HIP FRACTURE

The ultimate determinants of fracture are bone strength and trauma. Bone strength is related to quality of bone, its architecture and its mass. These characteristics cannot easily be assessed in-vivo, but correlate closely with bone mineral density (BMD). BMD can be measured safely, accurately and precisely by a number of methods. The most widely available of these is dual-energy X-ray absorptiometry (DXA). The clinical value of bone densitometry depends on its ability to estimate the risk of fracture. This section describes the developments in measurement techniques, determinants of peak bone mass in men and reviews the little evidence available in literature of BMD as a risk factor for hip fracture in men.

1.4.1 Measurement techniques

There are a number of techniques available for measuring BMD and these are summarised below.

1.4.1.1 Single Photon Absorptiometry (SPA)

Cameron and Sorenson first described SPA in 1963 (Cameron and Sorenson, 1963). Instruments based on this knowledge were commercially available through the 1970s and 1980s. An essential part of our knowledge of bone mineral content of the peripheral skeleton was obtained with these instruments. In SPA, instrument source and detector are coupled in parallel opposed geometry and are motor driven in a direction exactly transverse to the longitudinal axis of the bone. As the beam scans across the bone the integrated attenuation of the photon beam is compared to the beam intensity of the adjacent tissue. The requirement for a uniform tissue absorber of constant thickness surrounding bone makes SPA unsuitable for bone mineral measurements in spine, hip or other parts of the trunk, where bone is surrounded by tissues of different composition and thickness. SPA is restricted to quantification of bone mineral in appendicular bones, most frequently the radius. Measurements of the bone mineral content (BMC) on long bones correlates highly with total skeletal bone mineral and with total body calcium. As a test for the clinical diagnosis of osteoporosis, SPA has been disappointing. Several studies have shown that 30% or more of the patients with vertebral crush fracture have normal BMC. This limited usefulness is true for measurements on the ultradistal radius as well as the calcaneous.

While SPA measurements on the radius and the calcaneous are still useful for epidemiological studies of bone mass or perhaps in screening large populations, in clinical practice, SPA has been replaced by DXA measurements of bone mineral on the axial skeleton.

1.4.1.2 Dual X ray Absorptiometry (DEXA)

This is the most widely available technique and performs measurements at the lumbar spine, proximal femur, forearm and whole body. In this technique attenuation profiles are recorded in two different energies. By multiplying the soft tissue attenuation at one energy by a constant the difference between the two profiles becomes zero over soft tissue areas.

The first equipment for measuring bone mineral in the spine was based on a dual energy isotope source in the late 1960s. The technique was referred to as dual energy photon absorptiometry (DPA). However, these instruments had several practical drawbacks mainly imposed by the use of radioactive isotopes as photon sources. Precision errors were 2-4% for spine measurements and the decreasing source strength due to isotope decay required complicated correction and quality control procedures.

DXA was introduced in 1987 and overcome most of these shortcomings. In DXA, dual energy X-rays are generated by an energy switching system (Hologic) or by rare earth filtered X ray sources (Lunar, Norland). Each system has its own limitation, which are however, of little practical importance when the instruments are used within their specifications.

By both systems the human body is considered a two compartments system: soft tissue (calculated as a uniform absorber by averaging soft tissue values for each pixel) and bone. Of all soft tissues in the body, fat more than other tissues, affects the calculated (average) consistency of this soft tissue compartment that surrounds bone. It is also assumed that soft tissue above and below the bone, where it cannot be separated from bone, is equal to that on both sides of the bone. Furthermore, it is assumed that this calculated soft tissue represents bone marrow. These assumptions are not strictly true when patients are measured, but they set the limits within which the measurements have to be performed. For DXA measurements on the spine, if the amount of fat overlying the spinal column is greater than on either side of the lumbar spine, BMD will be

underestimated. A mean fat thickness of 2 cms results in bone mineral error of 9-10%. A change in bone marrow fat of 50% will change BMD by 5 - 6% (Sorenson 1990). More recent studies of DXA measurement accuracy found similar errors for BMC as well as area measurements, but smaller errors for BMD. Short term DXA precision error in-vivo of the lumbar spine, femoral neck, Wards' triangle and trochanter region is about 0.9, 1.2, 2.7 and 2.4% respectively. Normative databases are generally created from cross-sectional studies. With old age, cross sectional studies show an increase in the population variance and a decrease or cessation of the age related bone loss. This probably reflects both local degenerative changes in the lumbar spine and selective mortality of more frail individuals.

The DXA technique is also applicable to bone mineral measurements in peripheral bones. These measurements can be made using the instruments commonly used for the spine and hip scans. A special device to position the forearm is supplied. At the distal radius the scans give comparable accuracy and precision as those with SPA.

The advantage of this technique is the higher beam intensity and more rapid scan, improved spatial resolution with easier identification of vertebrae, and better precision. Recent developments in the technology includes scanning of the lumbar spine in the lateral position, which has the advantage of eliminating the posterior arch and the spines of the vertebral bodies, as well as aortic calcification, from the measurements. In addition the technique can be modified to assess vertebral heights, so that vertebral deformity can be quantified as part of the analysis of the scan. The precision of these recent additions remains uncertain.

Absorptiometric methods of bone density measurements can be reported in a variety of ways. The scan itself assesses the bone mineral content (BMC) and the area of the bone projected on the scan. Bone mineral density (BMD) is calculated as BMC/area. Finally, it is possible to estimate volumetric bone density (BMAD) using a mathematical algorithm. All these parameters are associated with the risk of fracture, but BMD is the variable with the closest association (Cummings *et al*, 1994)

1.4.1.3 Quantitative Computerised Tomography (QCT)

Quantitative computed tomography can be performed on the lumbar spine with most commercial instruments and with dedicated instruments on peripheral bones, generally

radius. It is the only method for assessing trabecular and cortical bone separately. The measurement unit is apparent density.

For measurements at the lumbar spine, a software package and calibration phantom to be added to the CT scanner are available. Several authors have reported marginally lower rates of bone loss with dual energy QCT, which corrects for the error due to fat. Bone density (QCT) shows a greater difference between normal and osteoporotic subject than areal bone density (DXA). Because of the greater normal population variance seen with bone density (QCT) meaningful comparisons between QCT and DXA should be based on Z scores. Of interest is also a comparison of the discriminatory ability of QCT and DXA to distinguish normal from osteoporosis. Expressed as percentage difference, the average difference was –20% (QCT) versus –11% (DXA). When expressed as Z scores, however, this was –0.7 versus –0.6 standard deviations.

1.4.2 Determinants of BMD in normal men

Although comparatively little attention has been paid over the years to the determinants of peak bone mass in men, race, genetic factors (Krall and Dawson-Hughes, 1993), hormonal factors, diet (Kelly *et al*, 1990) and exercise (Snow-Harter *et al*, 1992) have all been shown to have an influence. As in women, genetic factors account for a substantial amount of the variation in peak bone mass, but the precise genes remain to be elucidated.

The most obvious influence on peak bone mass is hormonal, and this is accounted for by the differences in pubertal development in males and females. Women exhibit a dramatic increase in bone mass during puberty, which is almost complete when puberty ends. Similar changes occur in men, but at a later time corresponding to the later onset of puberty, and peak bone mass is consequently achieved at a later age. The greater peak bone mass in men is largely related to body size rather than to BMD (Orwoll and Klein, 1995) except at certain sites such as the radius (Kelly *et al*, 1990). The age of pubertal onset may be important in determining peak bone mass. It has been shown that males with constitutional delay of puberty have substantially lower spine and forearm BMD than those with a normal onset of puberty, despite matching the two groups for length of post pubertal exposure to testosterone (Finkelstein *et al*, 1992). After reaching peak bone mass men maintain a stable bone density during middle age but then loose bone at an accelerating rate into old age (Tobin *et al*, 1993).

1.4.3 Age related bone loss in normal men

Bone loss occurs with ageing in men as in women, and longitudinal studies suggest that this loss may reach 5-10% per decade (Orwoll *et al*, 1990). This is greater than that estimated from cross sectional studies (Hannan *et al*, 1992). The change in bone density with age in men is of a similar order using single photon absorptiometry (Christian *et al*, 1989), dual photon absorptiometry (Mazess *et al* 1990), and by dual energy X-ray absorptiometry (Wishart *et al,* 1995; Burger *et al,* 1994; Mazess *et al,* 1990). Overall loss of peak bone mass from 20 years to advanced old age may reach 5-15 % for cortical bone and 15-45% for trabecular bone (Francis *et al*, 1989; Mazess *et al*, 1990). The rate of change of bone density with age varies at different sites. Most workers have found no significant change in bone density with age at the lumbar spine and trochanter (Mazes *et al*, 1990; Burger *et al*, 1994; Nguyen *et al*, 1994; Wishart *et al*, 1995). On the contrary, highly significant falls with age in femoral neck and Ward triangle BMD have been observed. A more recent study (Wishart *et al*, 1995) showed minimal loss of bone in men before age of 50 after which it appears to accelerate associated with a decline in markers of bone turnover. This bone loss is associated with histomorphometric evidence of decreased bone formation with decreased osteoid seam width and trabecular width (Aaron *et al*, 1987; Francis *et al*, 1989). Trabecular number may also be decreased and trabecular connectivity reduced (Mosekilde 1989), while bone turnover may be increased in elderly men (Orwoll and Deftos, 1990).

Up to 40% of men with severe osteoporosis have no identifiable medical condition or risk factor associated with bone loss (Francis *et al*, 1989; Baillie *et al*, 1992) and in such men with primary osteoporosis the pathogenesis of age-related bone loss is far from clear. Although genetic factors partly determine peak bone mass, they do not appear to be important in age-related bone loss in men (Christian *et al*, 1989). There have been some reports that men with osteoporotic fractures have hypercalciuria (Zerwekh *et al*, 1992; Kelepouris *et al*, 1995), but it is unclear whether this is due to increased bone resorption or renal leakage of calcium. It has been suggested that a combination of declining renal function and vitamin D deficiency during normal ageing may produce secondary hyperparathyroidism and consequent loss of bone (Orwoll *et al*, 1986). Increasing levels of serum parathyroid hormone with age have been implicated in age-related bone loss in men (Orwoll *et al*, 1986), as have decreasing serum growth hormone levels (Johansson *et al*, 1994).

A variety of other factors may influence age-related bone loss, including low vitamin D levels (Orwoll *et al*, 1986), low serum testosterone levels (Kelly *et al*, 1990; Kelepouris *et al*, 1995; Murphy *et al*, 1993), and low calcium intake (Kelly *et al*, 1990) and absorption (Francis *et al*, 1989). Other studies however, have shown little if any correlation between BMD at various sites and free testosterone levels (Drinka *et al*, 1993) or dietary calcium intake (Francis *et al*, 1992). A longitudinal study on healthy male twins addressed the issue of genetic and environmental factors in determining rate of bone loss in men over a 16 year period (Slemenda *et al*, 1992). The study showed both cigarette smoking and alcohol consumption to be the independent predictors of bone loss. Intense physical activity was also associated with slightly reduced bone loss. Rates of bone loss were similar within twin pairs, apparently because of shared environment, making it difficult to separate genetic from environmental effects on rate of bone loss.

1.4.4 BMD as risk factor for hip fracture

Bone mineral density (BMD) is highly correlated with bone strength (Mazess *et al*, 1982), accounting for 75-85% of the variance in ultimate strength of the bone tissue (Melton *et al*, 1988). Studies in women indicate that for each standard deviation reduction in bone mass the risk of hip fracture increases by a factor of 1.5-3.0 (Marshall *et al*, 1996). Less is known about the influence of BMD in determining fracture risk in men. Several observational studies suggest that BMD is lower among men who have sustained a hip fracture than those without, though in most of these the number of individuals studied have been relatively small (Karlsson *et al*, 1993; Greenspan *et al*, 1994; Greenspan *et al*, 1998; Nguyen *et al*, 1996; Boonen *et al*, 1997; Nyquist *et al*, 1998; Melton *et al*, 1998; De Laet *et al*, 1998).

Bone mineral density diminishes with ageing in the femoral neck, falling an estimated 39% in men between the ages of 20 and 90 years, while BMD of the intertrochanteric region of the proximal femur declines 35% (Riggs *et al*, 1982). Age-related bone loss in the shafts of the limbs is partially compensated for, biomechanically, by remodelling of these bones to increase the diameter, and thus increase resistance to bending and torsion. This process is less marked at the ends of these bones where the fractures occur that are typically associated with osteoporosis. There is little compensatory increase in diameter of the proximal femur to offset cortical bone loss with ageing (Melton *et al*, 1988).

Consequently, the age-related reductions in bone mass leads to a corresponding decline in strength of the proximal femur, which is greater in women than men.

Since bone strength is a determinant of fracture susceptibility, it follows that BMD is also correlated with fracture risk. There is now ample evidence that bone mass measurements can stratify patients on the basis of fracture risk. Recently published studies have demonstrated that measuring bone mass at the radius (Hui *et al*, 1988) or calcaneum (Wasnich *et al*, 1987) will predict the risk of fracture in the future. In contrast to extensive studies in women, few studies have related BMD in men to the risk of hip fracture. Studies have shown that there is a gradient of increasing hip fracture risk as bone mass falls. In a group of 654 men in Malmo in whom BMD was assessed by single-photon absorptiometry, those in the lowest quintile of BMD had a 6-13 fold increase in risk of fracture over the following 11 years (Gardsell *et al*, 1990). A later study from the same centre using a case control design compared BMD using DEXA within 10 days of hip fracture to controls (Karlsson *et al*, 1993). Of their 93 hip fracture cases, 26 were men with mean age of 75 years. They found significantly lower BMD at both the lumbar spine and the proximal femur in the hip fracture patients compared to age and sex matched controls. A 66% reduction in risk of hip fracture (n=31) per SD increase in BMD at the femoral neck was reported on prospective follow-up of 820 men, aged 60 or more, residents of DUBBO city (Australia), over a 2 year period (Nguyen *et al*, 1996). This finding is in agreement with previous studies in women (Cummings *et al*, 1990) and supported by reports of a 3 fold increase in risk of fracture per SD decrease in BMD in men (De Laet *et al*, 1998). Measurement at the proximal femur was a more powerful predictor of fracture risk than the lumbar spine site consistent with findings of some (Cummings *et al*, 1993) but not all researchers (Melton *et al*, 1993). In the elderly, femoral BMD is more sensitive than lumbar spine. Another prospective population - based study assessing predictors of hip fracture risk in white men (NHANES) aged 45-74 years showed that phalangeal bone density was inversely related to hip fracture risk. In both the age- and risk-adjusted models, fracture risk increased by 70% for each 1 SD decrease in bone density (Mussolino *et al*, 1998). The drawback of this study was the determination of BMD from a baseline X-ray of the left hand using radiographic absorptiometry (RA) and in the small number of fracture cases (n=71 hip fractures). The authors concluded that the relative risks for phalangeal BMD and hip fracture risk in their study was similar to those seen for other appendicular sites using a variety of bone

densitometry techniques. A recent prospective population - based study was carried out on a cohort of 242 men, aged 50-80 years who were followed for a period of 7 years with a total of 9 hip fractures during the study period (Nyquist *et al*, 1998). This study concluded that using SPA, a 1 SD decrease in forearm BMD is associated with a relative risk of osteoporotic fracture 1.75 95%CI (1.08-2.83); and relative risk of hip fracture 3.88 95%CI (1.3-11.57). The only prospective study addressing this issue in elderly nursing home residents, including 7 men with a hip fracture, similarly showed significantly lower femoral BMD in subjects who fell and fractured compared to those who fell but did not sustain a fracture (Greenspan *et al*, 1998). The same authors in an earlier study assessed site - specific BMD in 112 elderly hip fracture patients including 27 men and concluded that a relatively lower trochanteric or a high femoral neck BMD was associated with trochanteric hip fractures (Greenspan *et al*, 1994). This led to suggestions of site specific measurements for assessment of fracture risk. Clearly therefore, using a range of measurement techniques and different study designs BMD seems to be an independent risk factor for fracture in men. This appears to be true for all types of fractures. These findings parallel those in women. However, contrary to the wealth of literature in women, studies in men are limited by the very small sample size, in particular number of hip fractures.

The WHO criteria for diagnosis of osteoporosis relate specifically to Caucasian women. The reference ranges currently used for men are those supplied by the instrument manufacturers, and often relate to smaller study population than those obtained for women. This may lead to inaccuracy in the reference ranges for men highlighting the urgent need to establish appropriate reference ranges for BMD in men.

1.5 SEX HORMONES AS RISK FACTORS FOR HIP FRACTURE

1.5.1 Background

This chapter outlines the patho-physiology of sex hormone production, changes in hormonal milieu with age, mechanism of action of sex steroids on target tissues with special emphasis on bone and finally provides evidence on the role of sex steroids, in maintaining skeletal health in men.

1.5.2 Brief review of the control of sex hormone production

1.5.2.1 In health

The control of testicular function begins with the pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. GnRH is transported by the hypothalamic-pituitary-portal system to the anterior pituitary, where it effects the release of luteinizing hormone (LH) and follicular stimulating hormone (FSH). The frequency of GnRH pulses seen by the pituitary along with the negative feedback signals is the determinant of the relative amounts of LH or FSH that are released from the pituitary. At a GnRH pulse frequency of 3.8 pulses every six-hour, optimal amounts of both LH and FSH are released for normal testicular function. If the pulse rate of GnRH slows, then FSH is preferentially released, while more rapid GnRH pulse frequency results in a more prominent release of LH. Following release from the pituitary gland, LH is transported via systemic circulation to the testes, where it specifically binds to the Leydig cells to initiate testosterone production and secretion. FSH after release into the systemic circulation binds specifically to the Sertoli cells in the testes and stimulates the secretion of a number of proteins. One of these is inhibin, which, along with testosterone from the Leydig cell, induces and maintains spermatogenesis. The secretion of FSH and LH is regulated by the negative feedback of testosterone and inhibin at the level of both the pituitary and the hypothalamus. Testosterone can inhibit the secretion of both LH and FSH, while inhibin inhibits primarily the secretion of FSH.

1.5.2.2 In disease states

Primary hypogonadism is the result of a testicular defect involving either the Leydig cell production of testosterone, seminiferous tubule production of sperm, or both compartments.

Secondary hypogonadotrophic hypogonadism is suspected when the end products, testosterone or sperm are low and there is no increase in LH or FSH.

Combined primary and secondary hypogonadism: Decline in gonadal function with age is multifactorial. It includes an increased negative feedback capacity of testosterone on LH secretion, decreased gonadotrophin response to GnRH, and decreased testicular response to human chorionic gonadotrophin (HCG). Recent studies examining frequent samples of testosterone throughout the day have shown that there is a significant decline in total testosterone because with age, in addition to the declining testosterone secretory capacity of the testes, there is also an age related increase in sex hormone-binding globulin (SHBG). Overall, associated with the decrease in testosterone with age there is an increase in LH and FSH suggesting that a primary testicular defect is predominant.

Severe stress or injury rapidly lowers serum testosterone and gonadotrophin levels. Even if the serum binding protein for testosterone is decreased, free levels of serum testosterone remain low. This effect appears to be due to an effect on gonadotrophin secretion with a decrease in immunoreactive LH as well as an even greater decrease in biologically active serum LH. Immediately following the onset of hospitalisation for an acute severe illness, there may be a period of hypogonadotrophic hypogonadism.

Isolated deficiency of LH is known and termed as the fertile eunuch syndrome. These men are androgen deficient but have enough FSH secretion to maintain fertility. One group that may fit this syndrome are older men who have fathered children and maintained spermatogenesis but have a lower than normal testosterone levels without an increase in LH. These men most likely fall on the curve of normal ageing.

Isolated FSH deficiency has also been reported. They have normal androgens but have decreased or absent sperms without concomitant increases in FSH.

1.5.3 Endocrine evaluation of testicular function

1.5.3.1 Testosterone

The laboratory diagnosis of hypogonadism begins with the finding of testosterone deficiency. The daily production of testosterone in adult men is approximately 6 mg, and the testosterone content of the adult testis is 15-25 ug, indicating that the testis is continuously synthesising and releasing testosterone into the circulation.

Testosterone is secreted in bursts at a frequency of approximately one pulse per hour. Testosterone varies in peripheral blood from 50-200 ng/dl but these variations do not correlate with the secretory bursts, partly because of the rapid frequency and the delayed disappearance of testosterone from peripheral blood because of binding to SHBG. Single measurements of testosterone levels in the morning reliably predict the annual mean level. There is a diurnal rhythm in the circulating testosterone levels in adult men, however, with highest levels in the morning, followed by a progressive fall throughout the day, reaching the lowest levels in the evening during the first few hours of sleep. Peak and nadir differ by approximately 30%. This diurnal rhythm is blunted with ageing and in testicular failure.

Commercial kits for direct assay of testosterone in unextracted serum use an I^{125}-labelled tracer which is simple to use and accurate for most purposes. In some assays the results may be artifactually overestimated with low SHBG levels and underestimated with high SHBG levels because of SHBG differences between levels in the standards and samples. In addition, direct assays tend to overestimate the true values of testosterone at very low concentrations. To control for effects of SHBG concentrations and to discriminate among low levels accurately, immunoassays using organic solvent extraction and chromatographic separation may be needed.

1.5.3.2 Sex Hormone-Binding Globulin

Of the circulating testosterone in normal men, less than 4% is free (not protein bound), 1-2% is bound to cortisol-binding globulin, approximately 40% is loosely bound to albumin, and the remainder is bound with high affinity to sex hormone-binding globulin (SHBG). SHBG is synthesised in the liver and released in circulation. The function of SHBG is partly to protect testosterone from rapid metabolic clearance. Findings of membrane binding sites

for SHBG in tissues (testis, prostate, epididymis and others) suggests that they could also play a direct role in androgen action.

SHBG is measured indirectly using radioligand-binding assays based on the specific binding of 3H-testosterone or by direct immunoassay of the protein. A number of disorders are associated with an increase or decrease of SHBG levels and must be borne in mind.

1.5.3.3 Free / Bioavailable Testosterone

When testosterone is measured by immunoassay, the total testosterone is determined. Abnormal SHBG levels, however, can cause an increase or decrease in the measured serum total testosterone concentrations. One approach to correct the total testosterone for the variation in SHBG is to determine a free testosterone index. It is calculated as the ratio of total testosterone/SHBG, or total testosterone times SHBG divided by the mean normal SHBG levels.

The level of free (non-protein bound) testosterone is independent of SHBG concentration. This is determined from the diffusion across a semipermeable membrane of tracer amounts of 3H-testosterone added to the sample. The free testosterone is calculated from the product of the total testosterone level and the percentage free testosterone. This method is complex, time consuming and expensive. Another approach is a solid phase free testosterone radioimmunoassay (RIA) kit that uses a ^{125}I-labelled testosterone analogue as the tracer. This has a strong positive correlation with free testosterone measured by equilibrium dialysis but produces substantially (75%) lower values making comparison with published data difficult.

Bioavailable or non -SHBG bound testosterone is the one that is bound loosely with albumin and is readily available to target tissues as is free testosterone. The most widely used technique to measure non-SHBG bound testosterone involves the precipitation of tracer amounts of 3H-testosterone bound to SHBG using ammonium sulphate. The bioavailable testosterone is calculated by subtracting the SHBG-bound from the total testosterone level.

1.5.3.4 Gonadotrophins

The major regulator of testosterone production is LH, which is secreted in adult men in pulses in response to bursts of gonadotrophin-releasing hormone (GnRH) released from the hypothalamic neurones into the hypothalamic portal blood. Because of the robust pulsatile pattern of LH concentration in peripheral blood, a single blood sample may not provide an accurate estimate of mean concentrations. Pooled assay of 3 samples drawn at 20-minute intervals may give a better estimate of the mean. Although follicular-stimulating hormone (FSH) as well as LH secretion is stimulated by GnRH, serum FSH levels are more constant in peripheral blood, presumably because FSH responses to GnRH are delayed, of lower magnitude, and because the clearance of FSH from blood is slow compared to LH.

If serum LH and FSH concentrations are increased, the diagnosis is primary testicular failure. They may have normal total testosterone although the bioavailable testosterone is usually low. The rise in LH levels reflects reduced testosterone negative feedback, whereas elevated FSH results from deficient secretion of inhibin as well as sex steroid. In some men LH and testosterone levels are normal, but FSH levels are elevated. This is believed to occur because seminiferous tubules are more sensitive to damage than are Leydig cells. A monotropic increase in serum LH is rarely seen. When testosterone deficiency is caused by impaired gonadotrophin secretion LH may be low or low normal. The overlap in serum LH levels between normal and hypogonadal men may be partly explained by the incomplete analysis of LH secretion that follows single blood sample, changes in LH bioactivity and by assay insensitivity at lower values. The diagnosis of gonadotrophin deficiency has been facilitated by the development of sensitive and specific two-site immunoassays. Even though LH levels measured by two-site immunoassays are generally low in hypogonadal men with hypothalamic or pituitary disease, the diagnosis of gonadotrophin deficiency should not be made by measuring the serum LH level alone, but a low serum testosterone level should also be documented.

1.5.3.5 Oestrogen's

Most of the oestrogen in the circulation in men are derived from the bioconversion of testosterone or androstenedione to oestradiol or estrone, respectively, by aromatase enzyme complex in fat, muscle, kidney and liver. Thus circulating oestradiol levels in men are

proportional to the production of these substrates and to the aromatase activity in tissues. Most of the oestradiol is loosely bound to albumin or unbound, and a small proportion is bound to SHBG. However, the affinity of SHBG for oestradiol is less than for testosterone, hence, changes in SHBG have lesser effect on total oestradiol compared to testosterone levels. Serum oestradiol levels are relatively constant throughout the day and unlike testosterone are maintained with ageing. Commercial kits for direct assay of oestradiol are available but are optimised for high values. At the low values characteristic of male plasma, these assays are imprecise and inaccurate and generally overestimate the true values. Determination in male plasma requires extraction with organic solvents before immunoassay.

1.5.4 Sex steroid changes with age in men

1.5.4.1 Testosterone

Both cross-sectional (Vermeulen 1991) and longitudinal studies (Morley *et al*, 1997) involving large groups have clearly provided evidence that the ageing process in man is accompanied by changes in the hypothalamic-pituitary-gonadal axis which results in notable decline in serum levels of androgens. Serum testosterone levels decrease by 30% between age 25 and 75 years. A recent meta-analysis of 88 published studies showed a significant inverse relationship between age and total testosterone (Gray *et al*, 1991). However, reports of age related declines in free testosterone are few and show an estimated annual decline of 1.2% in free testosterone and 1% in albumin bound testosterone with age. The steeper decline of free than total testosterone is explained by an age-associated increase in SHBG (Vermeulen *et al*, 1972). The only prospective population based study (Rancho-Bernado) involving 810 men over the age of 24-90 years showed a weaker association of total testosterone (r=-0.13) than bio-available testosterone (r=-0.52) with age (Greendale *et al*, 1997). This dramatic decrease was independent of body size, health behaviour and chronic disease. In view of the expanding role of androgens in bone remodelling, these changes might be involved in the determination of fractures in older men.

1.5.4.2 Oestradiol

Studies relating oestradiol and ageing in men are few and have produced mixed results. Some report no age association with oestradiol (Tenover *et al*, 1987) while others have reported reduced levels with age (Khosla *et al*, 1998). In the Rancho Bernado Study, mean total oestradiol declined but not significantly with age. In contrast, a strong negative association (r=-0.28) of bioavailable oestradiol with age was seen and was explained by decreasing levels of testosterone, the primary substrate for male oestradiol, coupled with a higher SHBG in older adults (Ferrini and Barrett-Connor, 1998).

1.5.4.3 Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone has drawn recent attention as a bio- marker of ageing. Shortly after birth DHEA production drops to unmeasurable levels within months. It remains low until the age of 5-6 years followed by a surge preceding puberty. It peaks at puberty then gradually declines throughout life at the rate of approximately 0.10-0.18 umol/l per decade reaching unmeasurable values after the age of 70 in many individuals.

1.5.5 Mechanism of action

1.5.5.1 General

Steroids enter the cell by diffusion. Inside the cell, testosterone is converted to more active metabolites by two enzymes: 5 alpha reductase and aromatase. 5 alpha reductase irreversibly converts testosterone to dihydrotestosterone (DHT) which is then converted to 5 alpha androstane -3 alpha, 17 beta-diol. Aromatase irreversibly converts testosterone into estrogenic molecules. Metabolism of testosterone to oestrogen compounds results in action via estrogenic receptors and conversion to DHT greatly increases binding affinity to androgen receptors. Testosterone and DHT bind to the same high affinity androgen receptor protein. This hormone receptor complex interacts with acceptor sites in the nuclei to effect a biological response. The result of the interaction within the chromosomes is increased transcription of specific target genes and subsequent appearance of new mRNA and protein in the cytoplasm.

1.5.5.2 On bone

Published studies have confirmed the presence of androgen receptors in bone cells and the ability of these cells to respond to androgens (Colvard *et al*, 1989). Effect on maintaining bone mass are thought to be both direct through action on osteoblast and chondrocytes and indirect through maintaining muscle mass and therefore loading on bone. Normal human osteoblast-like cells have been shown to express functional androgen and oestrogen receptors (Colvard *et al*, 1989). This is consistent with the fact that men have both hormones in circulation. It is postulated that oestrogen is a possible intracellular receptor in men (Nawata *et al*, 1995). Androgens increase osteoblast transforming growth factor-beta (TGF-β) production, elevate levels of insulin growth factor-II (IGF-II) receptors and increase sensitivity to fibroblast growth factor. They also increase osteoblast differentiation based on alkaline phosphatase and collagen production. In addition, there is evidence that androgens act on osteoblast to produce autocrine/paracrine factors such as growth hormone, IGF-I or decrease production of interleukines (IL-1 & IL-6). These would increase bone mass via stimulating bone formation or resorption or both.

1.5.6 Role of testosterone in influencing bone density

Animal studies have mostly been performed in orchidectomised male rats. There is reservation about the appropriateness of this model because rat skeleton, unlike humans, grows throughout life. Therapy with testosterone or 5 alpha DHT has shown to increase bone mass, though it remains lower than in control rats (Coxam *et al*, 1996).

A number of studies in men have addressed the relationship between androgen status and bone density. Most studies carried out on *healthy men* living in community have shown a positive correlation between androgen levels and BMD. Rudman and co-workers (Rudman *et al*, 1994) compared the relationship between testosterone and BMD in healthy men living freely versus living in care. Testosterone was the most important predictor of BMD in free living men even after multivariate analysis including age. In contrast, amongst men living in care, although testosterone correlated to BMD at the femoral neck it failed to reach significance after age was entered into the equation. Similarly, a cross sectional study comparing young (age 20-40 years) versus older (age 60-90 years) healthy men reported a positive correlation between BMD (percent cortical area at II phalanx) and testosterone

(Foresta *et al*, 1984). Another cross sectional study of 90 healthy men over a wide age range (20-80 years) supported this observation by confirming a significant positive correlation between free testosterone and BMD at all sites (Ongphiphadhanakul *et al*, 1995). The relationship persisted even after adjusting for age. In contrast, another cross sectional study on ambulatory elderly men including some with diseases (Drinka *et al* 1993) failed to show an association between free testosterone and BMD.

Studies addressing the effect of *androgen deficiency in early life* to attainment of peak bone mass have shown consistent results. Compared to normal, significantly lower spinal and radial BMD have been reported in men with history of delayed puberty (Finkelstein *et al*, 1996). Prospective follow-up after 2 years confirmed permanent decreased peak BMD in these men despite evidence of normal bone turnover. Similar findings of low BMD in men with established hypogonadism have been confirmed by other researchers (Francis *et al*, 1986; Arisaka *et al*, 1995). Significant increase in BMD following therapy with androgens in both hypogonadal (Francis *et al*, 1986) and eugonadal (Anderson *et al*, 1996) men also point towards the role of androgens as important determinants of bone health. Furthermore, clinical studies have shown that castration results in enhanced incidence of osteoporosis in men and treatment with androgens prevents its occurrence. Twelve men who underwent judicial castration for sexual delinquency showed significant decline in lumbar spine BMD with the most rapid loss occurring in the first five years after castration (Stepan *et al*, 1989).

The role of hypogonadism in the *causation of osteoporotic fractures* in men is still unclear. Biochemical evidence of hypogonadism has been reported in about 20% of men with vertebral fractures (Baillie *et al*, 1992) and upto 50% of men with hip fractures (Stanley *et al*, 1991; Jackson *et al*, 1992). However, these studies are limited by small numbers, heterogeneity in timing of sample collection (Jackson *et al*, 1992), selection of control population (Stanley *et al*, 1991) and absence of BMD measurement (Stanley, *et al*, 1991; Jackson *et al*, 1992; Abbasi *et al*, 1995). Assessment of hypogonadism based on chart reviews with their inherent problems of accuracy and completeness furthermore cast doubt on the authenticity of the results (Stanley *et al*, 1991; Abbasi *et al*, 1995). The recent case-control study reporting hypogonadism in men with an osteoporotic hip fracture (Boonen *et al*, 1997) is limited in controlling for the effects of trauma due to proximity in sample

collection to fracture event and its cross sectional design. In addition, the authors restricted BMD measurements to the proximal femur. The only prospective population- based study addressing this issue in men failed to show a correlation between testosterone and BMD (Nyquist *et al*, 1998). The main limitations of this study was the very low number of fractures, especially hip fractures (n=10), in addition to use of SPA for BMD measurements at the forearm.

This combination of clinical and experimental evidence has led to the current view that gonadal androgens are the principal bone-active steroid hormones in men and androgen deficiency is thought to play an important role in many cases of male osteoporosis. Although decreased androgen levels have been linked to lower bone density in men, there is no definite proof that there is a link between lower androgen levels and the increased incidence of hip fractures.

1.5.7 Role of oestradiol in influencing bone density

Oestrogen deficiency is an important pathogenic factor in female osteoporosis. It is also known that androgens have a strong anabolic effect on bone (Orwoll 1996), on human osteoblastic cells *in vitro* (Kasperk *et al*, 1997), as well as in hypogonadal (Greenspan *et al*, 1986) and eugonadal men *in vivo* (Anderson *et al*, 1997). This effect has been suggested to be partly due to aromatisation of androgens into oestrogens. Androgen receptors and 5 alpha reductase are found in osteoblasts at densities consistent with other androgen - sensitive tissues, with similar binding affinities (Orwoll *et al*, 1991; Benz *et al*, 1991; Vanderschueren and Bouillon, 1995). Oestrogen receptors are equally abundant in cultures of these cell lines (Colvard *et al*, 1989; Benz *et al*, 1991) and osteoblasts respond metabolically to oestrogen *in vitro* (Purohit *et al*, 1992) and in fresh biopsy samples of male bone (Baris *et al*, 1996). Aromatase activity is present in cultured osteoblast cell lines (Purohit *et al*, 1992) demonstrating that these cells have the capacity to convert testosterone to oestradiol. In orchidectomised rats oestradiol prevents bone loss more effectively than progestogen or 5 alpha-DHT, although the combination is more effective than any single agent (Coxam *et al*, 1996).

In humans, skeletal oestrogen dependency is supported by a number of small studies and key case reports. A number of studies on groups of *healthy* men have shown that bone densities at the lumbar spine, femoral neck, trochanter and radius are positively correlated to serum oestradiol concentrations. A significant positive correlation between estrone and percentage cortical area measured at the second phalanx was demonstrated in a cross sectional study of healthy young and older men (Foresta *et al*, 1984). On similar lines, another cross sectional study involving 37 healthy men found that BMD at both lumbar spine and hip correlated more closely with oestradiol levels (r=0.38) than with testosterone (r=0.24) (Anderson *et al*, 1998). A prospective study of 93 healthy men aged over 65 years revealed serum oestradiol levels to be closely related to initial BMD values at all sites and predictive of significantly lower rates of bone loss at hip and radius over a 2 year period (Slemenda *et al*, 1997). Further, in two recent studies (Greendale *et al*, 1997; Khosla *et al*, 1998) it has been shown that oestrogen/SHBG ratio is an independent predictor of BMD in healthy men.

There is dearth of literature on the role of oestradiol in men with osteoporotic *fracture*. Using a case-control study design, lower oestradiol levels were found in men with a vertebral fracture compared to controls (Francis *et al*, 1989). The small size of the study implied that differences observed did not attain statistical significance. A similar case-control study showed men with idiopathic osteoporosis (n=12) to have significantly lower serum levels of oestradiol and oestradiol/ SHBG ratio compared to aged matched controls (Gillberg *et al*, 1999). The authors also showed femoral neck BMD to bear a significant and positive correlation with ratio oestradiol/ SHBG (r=0.67). In a therapeutic trial of testosterone supplementation in men with osteoporotic vertebral fracture, pharmacological doses of testosterone were associated with rises in oestradiol levels. The increase in lumbar spine BMD noted correlated more closely with changes in oestradiol levels than serum testosterone (Anderson *et al*, 1997). The only published study evaluating oestradiol in men with hip fracture did not show any differences in oestradiol levels between fracture cases and healthy controls (Boonen *et al*, 1997).

In case reports describing genetic mutations, men with defective aromatase activity (Morishima *et al*, 1995; Carani *et al*, 1997) and non functional oestrogen receptors (Smith *et al*, 1994) showed markedly reduced BMD despite normal or raised testosterone levels

and normal androgen receptors. Perhaps the most convincing evidence is the case of a 28 year old man with an inactivating mutation of his aromatase gene who presented with infertility, eunuchoid habitus, non closure of epiphyses, below average BMD and bone age of 15 years. Treatment with testosterone replacement produced no benefit but treatment with oestradiol resulted in skeletal maturation, rapid increase in lumbar spine BMD and epiphyseal closure (Carani *et al*, 1997).

1.5.8 Role of DHEA in influencing bone density

Recently there has been considerable interest in the role of DHEA and its sulphate in the prevention of age related diseases such as osteoporosis. Human osteoblasts have been shown to convert DHEA into estrone (Nawata *et al*, 1995), which is a precursor for both testosterone and oestradiol. DHEA itself is known to act directly on androgen receptors of osteoblasts to stimulate proliferation and differentiation (Kasperk *et al*, 1997). The role of DHEA in the maintenance of male bone mass has received limited investigation. The Rancho Bernado Study involving 534 men (and women) failed to establish a correlation between DHEA and BMD at any site in men (Greendale *et al*, 1997). Two previous studies similarly failed to show an association (Murphy *et al*, 1993; Barrett-Connor *et al*, 1993).

1.6 VITAMIN D, PARATHYROID HORMONE AND CALCIUM AS RISK FACTORS FOR HIP FRACTURE

1.6.1 Background

Many factors contribute to the bone loss that characterises the syndrome of osteoporosis. This section focuses on the evidence in literature supporting the potential involvement of the two major calcium-regulating hormones, parathyroid hormone (PTH) and vitamin D, in the development of osteoporosis.

Among the many functions that parathyroid hormone and Vitamin D perform, the most important is maintenance of normal bone remodelling. Osteoporosis is an intrinsic outcome of the ageing process. Also, intrinsic to the ageing process is the synthesis, metabolism, and responsiveness of vitamin D and parathyroid hormone. It is possible that age related changes in vitamin D and parathyroid hormones are causally related to the age-associated changes in bone mass. The following section discusses the various mechanisms that may be responsible for derangement of the normal calciotropic hormonal environment with age.

1.6.2 Overview of calciotropic hormones in the pathogenesis of osteoporosis

Subclinical deficiency of vitamin D has long been recognised to be a factor in the development of osteoporosis. Most studies report a fall in circulating concentrations of the active form of vitamin D (1-25 dihydroxyvitamin D) with advancing age. Osteoporotic individuals have circulating 1-25 dihydroxyvitamin D levels that are even lower. Possible abnormalities include vitamin D deficiency, abnormal production of 25-OH D or 1-25 dihydroxy-vitamin D, altered sensitivity / number of intestinal vitamin D receptor or acquired resistance to vitamin D.

Inadequate supply of vitamin D from its two major sources, diet and sunlight, can lead to the disorder. Vitamin D is derived from dietary sources and via supplementation in milk in some countries. In addition to low dietary intake it is known that absorption of vitamin D from the gastrointestinal tract is reduced upto 40% with advancing age. Whether there is a gender difference in dietary vitamin D absorption rate is not known. Also, whether the

absorption rates vary between subjects who develop osteoporosis and their age/ sex matched controls is not known.

The other source of vitamin D is the skin, where Ultraviolet B energy of 290-315 nm converts 7-dehydrocholesterol to previtamin D. 7-dehydrocholesterol levels in the skin fall approximately 50% between 20-80 years of age. It is not known whether the reduced quantity of skin substrate is exaggerated in those who develop the disease. Studies have shown a seasonal variation in levels of 25 OH D. In winter months at northern latitudes, decreased exposure of skin to UV light of correct wavelength can lead to vitamin D insufficiency. Recent studies have shown that no synthesis of pre-vitamin D occurs in the skin during late fall and winter months at northern latitudes resulting in subclinical vitamin D deficiency. In parallel, bone density has been observed to decline during these months, rising again in summer. The rise in bone density has been seen to be associated with a resolution of the accompanying secondary hyperparathyroidism.

Subclinical vitamin D deficiency has been seen in sub-population of osteoporotic patients. These subjects do not exhibit symptoms of vitamin D deficiency. On investigation, they are found to have low mean bone mineral density, low serum calcium and phosphorus, higher parathyroid hormone and urinary calcium excretion than vitamin D replete subjects. Secondary hyperparathyroidism induced by vitamin D deficiency is seen as the major factor leading to low bone density. Studies attempting to implicate subclinical vitamin D deficiency in the development of osteoporosis have assayed levels of 25-OH D levels. These are believed to be an accurate representation of the storage form of the vitamin and hence useful in clinical practice.

There is no evidence in literature that the liver looses its capacity to convert vitamin D to 25- hydroxyvitamin D with ageing and in osteoporosis. On the contrary, a decline in the ability of the kidney to form 1-25 dihydroxyvitamin D occurs with age. The age-related decline in renal 1 alpha-hydroxylase activity has been proposed as a mechanism of age-related osteoporosis. The decline in renal hydroxylation capacity associated with advancing age could be due to the ageing process per se or to the decline in renal function seen in the elderly. Halloran and his colleagues studied 70 men with normal renal function and

demonstrated normal ability of the kidney to convert 25-OH D to 1-25 dihydroxyvitamin D. They concluded that the impaired responsiveness is due exclusively to a decline in renal function with age (Halloran *et al*, 1990). Studies comparing 1-alpha-hydroxylation capacity between normal and osteoporotic subjects have not been able to show any difference.

Another possible role of vitamin D in the pathogenesis of osteoporosis may be reduced sensitivity to 1-25 dihydroxyvitamin D in the small intestine. Intestinal resistance to 1-25 dihydroxyvitamin D is proposed as a primary alteration. Alterations in binding of 1-25 dihydroxyvitamin D to its receptors in the small intestine and/or reduction in intestinal sensitivity to 1-25 dihydroxyvitamin D due to age related reduction in vitamin D receptor concentrations are proposed mechanisms resulting in osteoporosis.

Genetic polymorphism of the vitamin D receptor has been proposed as a determining factor for the development of osteoporosis. Although initial studies were very favourable, later research has not been conclusive. Whether these allelic variants are markers for other more relevant genetic factors is yet unknown.

The importance of the various mechanisms by which alterations in vitamin D system can lead to osteoporosis is yet unclear. Any or all the above mentioned mechanism may play a part contributing to bone loss with ageing. Impaired calcium absorption from the gastrointestinal tract due to abnormalities at any point in the synthesis, metabolism and responsiveness to vitamin D, underlie the potential role of vitamin D in the development of osteoporosis. These result in calcium deficiency resulting in an imbalance between bone formation and resorption manifesting as osteoporosis.

The current consensus redefining vit D deficiency in relation to its bone effects is as follows:

Amount (ng/ml)	**(nmol/l)**	**Vitamin D status**
0-5	0-12	Severe deficiency
6-10	13-25	Mild deficiency
11-20	26-50	Sub-optimal supply (insufficiency)
21-100	51-250	Optimal supply
101-150	251-375	Highest levels obtained after long-time UV light exposure
>150	>375	Intoxication

1.6.3 Vitamin D in normal elderly men

Vitamin D status was assessed in an adult urban French population of 1569 subjects including 765 men aged 45-65 years (Chapuy *et al*, 1992). Vitamin D insufficiency (<12 ng/ml) was found in 14% of this healthy population. 74% of the men had serum 25-OH D levels lower than 31 ng/ml, the threshold at which secondary hyperparathyroidism sets in. This study concluded a very high prevalence of vitamin D insufficiency in the general adult population of France. The researchers did not find an age or sex effect on 25-OH D values between 35-65 years. Vitamin D levels related to latitude of residence and hours of sunshine. Similar results were reported in another study among Swiss adults (Burnand *et al*, 1992). The authors found that 34-95% had a relatively low concentration of vitamin D (i.e. < 38 ng/ml or < 95 nmol/l) and 6% of the population was vitamin D deficient (< 20 nmol/l). Contrary to continental Europe, in North American men a very low prevalence (0.43%) of low 25-OH D (<12 ng/ml) was reported (Gallagher *et al*, 1998). This difference could be explained on the basis of better sunlight exposure and supplementation of dairy produce in the US.

These studies conclude that vitamin D insufficiency with resultant sub-optimal calcium absorption and secondary mild hyperparathyroidism is very common in elderly people (including men) particularly in Europe where dairy products are not fortified with vitamin D.

1.6.4 Effect of age and sex on Vitamin D status

Most (Agnusdei *et al*, 1998; Diamond *et al*, 1998; Rudman *et al*, 1989) but not all (Gallagher *et al*, 1998) studies addressing this issue have shown a decline in serum levels of vitamin D with age in men.

Using a cross sectional design age related changes in serum 1-25 dihydroxyvitamin D, PTH levels, intestinal calcium absorption and bone mass were studied in 70 normal men aged 17-91 years (Agnusdei *et al*, 1998). The study demonstrated that in normal males, after age 40years, both intestinal calcium absorption and levels of 1-25 dihydroxyvitamin D exhibit an age-related linear and progressive decrease. In parallel, an age-related increase in PTH (confirming hyperparathyroidism developing with ageing) was also noted. Similar decline of 25-OH D levels with age in men have been shown by other workers (Rudman *et al*, 1989).

Similar negative correlation's between age and serum 25-OH D levels (r = - 0.29) have been seen using a case-control study design (Diamond *et al*, 1998).

In contrast, in a cohort of 273 men and 814 women, aged 65-87 years, in different geographic sites in North America no relation of 25-OH D and serum PTH with age in men (r = 0.003) or women (r = - 0.03) was observed (Gallagher *et al*, 1998). The covariates predictive of 25-OH D were gender, season, calcium intake and weight. Similarly for PTH the covariates were 25-OH D, age, calcium intake and weight. Overall comparison by gender showed mean serum 25-OH D was significantly higher in men compared to women with a significant decrease in mean serum PTH in men compared to women. Serum PTH in men was inversely correlated with serum 25-OH D (r = - 0.25) and calcium intake (r = - 0.15).

1.6.5 Relationship between Vitamin D and BMD in men

Results of published literature so far are inconsistent and raise the need of large prospective studies exclusively addressing this problem in men. In a cross sectional study of 70 normal males, a decrease in vertebral and forearm BMD with advancing age after the age of 50 years, was reported (Agnusdei *et al*, 1998). The study also showed age-related linear reduction in vitamin D levels and intestinal calcium absorption. The study concluded that bone loss accelerates in men after 50 years of age and among other factors vitamin D levels play a role. On similar lines, Gallagher *et al* in the study mentioned earlier, showed that in men spinal BMD was positively correlated with serum 25-OH D (r=0.20), but not with serum PTH (Gallagher *et al*, 1998). In contrast, BMD at the femoral neck was not correlated with serum PTH or 25-OH D. Sherman and colleagues studied a highly motivated healthy cohort of 192 men and 120 women and evaluated the relationship between 25-OH D, 1-25 dihydroxyvitamin D, PTH and BMD in the radius, spine and femur. There was no significant associations between BMD at any site and serum concentrations of any parameters except in older men where lower radial BMD was significantly correlated with higher PTH and lower 25-OH D (Sherman *et al*, 1992). Factors that determine BMD at axial and appendicular sites were studied in 48 healthy men aged 21-79 years (Kelly *et al*, 1990). Dietary calcium intake was a significant independent predictor of BMD of axial

bones, explaining 24-42% of the variance at the lumbar spine and femoral neck respectively. Vitamin D levels were not measured.

Results from supplementation studies are more consistent and give some evidence of a positive correlation between vitamin D - calcium and BMD. The effects of 3 years of diet supplementation with calcium and vitamin D on bone mineral density, biochemical measures of bone metabolism and incidence of non vertebral fractures was studied in 176 men and 213 women, 65 years of age and older, living at home (Dawson- Hughes *et al*, 1997). The study subjects received 500-mg calcium (calcium citrate malate) plus 700 IU of vitamin D_3 per day or placebo. BMD was measured by DXA; blood and urine analysed every 6 months and non-vertebral fractures recorded. Differences in BMD were found between the calcium-vitamin D and placebo groups at all sites after one year, but were only significant for total body BMD in second and third years. Serum osteocalcin concentrations were 9% lower in men and 14% lower in women than at baseline, indicating that supplementation led to a sustained reduction in the rate of bone remodelling. In addition there were significantly reduced number of fractures in the calcium-vitamin D group. The study concluded that dietary supplementation of calcium-vitamin D moderately reduced bone loss over a 3-year period and reduced the number of non-vertebral fractures among community dwelling elderly.

On the contrary, an earlier study using a similar regime in men did not reveal any benefits on BMD (Orwoll *et al*, 1990). It may be that subjects in this study were younger (aged 30-87 years) and had a higher mean calcium intake than those in the study by Dawson Hughes and co-workers (1159 vs. about 700 mg per day).

The magnitude of the reduction in number of fractures observed in the study by Dawson Hughes (Dawson- Hughes *et al*, 1997) is similar to that reported in a study of 3270 elderly French women treated with 1200 mg calcium plus 800 IU of vitamin D or placebo (Chapuy *et al*, 1992). In contrast, in a study of 2600 elderly Dutch men and women, given 400 IU vitamin D daily (without calcium) as compared to placebo, no reduction in incidence of fractures was noted (Lips *et al*, 1996). This may raise the question about the individual

effects of calcium and vitamin D on BMD and fracture prevention and the therapeutic dose required in relation to latitude of residence.

1.6.6 Vitamin D as a risk factor for hip fracture in men

A number of cross sectional studies have in the recent past determined the role of vitamin D deficiency as a risk factor for hip fracture in elderly men. Most have consistently shown low vitamin D status in men with hip fracture compared to controls. Two researchers (Diamond *et al*, 1998; Boonen *et al*, 1997) have exclusively addressed this issue in men using small numbers (n = 41 and 40 respectively).

Vitamin D status was assessed in 41 Australian men consecutively presenting with a hip fracture and comparisons made with an equal number of two control groups: in-patient and out-patient (Diamond *et al,* 1998). Men with hip fracture had significantly lower 25-OH D levels than both control groups. Subclinical vitamin D deficiency (< 50 nmol/l) was present in 63% of fracture cases compared to 25% of the controls. In multiple regression analysis, subclinical vitamin D deficiency was the strongest predictor of hip fracture in their group of elderly men. Secondary hyperparathyroidism (>8.5) was seen in 17% of men with hip fractures compared with only 4.2% of controls. Their study concluded that subclinical vitamin D deficiency might contribute to the development of hip fracture through the effects of secondary hyperparathyroidism.

Similar results were seen in a cross sectional study involving 40 Swedish men, mean age 73 years, with a hip fracture (Boonen *et al*, 1997). Vitamin D levels were significantly lower in hip fracture cases compared to controls. Serum PTH was markedly increased in fracture cases. The study concluded that hypovitaminosis D may predispose to bone resorption in elderly men and increase risk of hip fracture.

Another group compared serum 25-OH D and parathyroid hormone in hip fracture cases (n = 179; men = 43) versus matched controls (Thiebaud D *et al*, 1997). In their group of 43 men with hip fracture, 25-OH D were significantly lower (-19%) than matched controls. 49% men with hip fracture had 25-OH D < 4.3 (lower limit of normal range). BMD was low in fracture cases, PTH correlated weakly with BMD (neck: r = - 0.19).

Similar results of low vitamin D status in hip fracture patients have been reported by other workers that have included men in their study although in small numbers (Harju *et al*, 1985; Lau *et al*, 1989; Ng *et al*, 1994).

There is only one randomised, placebo controlled clinical trial looking at effects on hip fractures and other peripheral fractures following vitamin D supplementation (400 IU/day) in a significant number of men (n=662) (Lips *et al*, 1996). Amongst 2578 Danish subjects (662 men) aged 70 years and above, over a period of 3.5 years, no difference in the incidence of hip or other peripheral fractures were noted between the two groups. It may be that the mean dietary calcium intake in the group was high. More studies of this nature are clearly needed.

1.6.7 Parathyroid function in the elderly

The cumulative response of a deficit in calcium intake (Chapuy *et al* 1987) and an age related decline in calcium absorption (Agnusdei *et al*, 1998), which is partially accounted for by 1-25 dihydroxyvitamin D deficiency (Recker, 1993), is a negative calcium balance stimulating PTH secretion (Hegarty *et al*, 1994). In addition, ageing is associated with a shift in basal calcium-regulated PTH secretion (Quesada *et al* 1992; Ledger *et al* 1994). The increase in PTH with age is not associated with an altered sensitivity of the parathyroid glands to extracellular calcium. Rather ageing is associated with higher basal and maximally stimulated PTH levels, similar to those described for patients with secondary hyperparathyroidism associated with renal insufficiency, and consistent with an increased number of parathyroid cells. In view of the fact that elderly women have normal responsiveness to 1-25 dihydroxyvitamin D suppression of PTH secretion (Quesada *et al* 1992; Ledger *et al* 1994), these parathyroid abnormalities do not seem to be related to parathyroid gland resistance to 1-25 dihydroxyvitamin D. More likely, the impairment of calcium balance with ageing provides a chronic stimulus to the parathyroid glands. This would result in age-related increase in circulating PTH.

Serum PTH has been reported to show a significant age related increase (Quesada *et al* 1992; Ledger *et al* 1994) although mean values remain within the normal range. This age related increase in intact PTH is partially determined by progressive decline in 1-25

dihydroxyvitamin D status, suggesting that age is associated with mild secondary hyperparathyroidism necessary to maintain normal serum 1-25 dihydroxyvitamin D concentrations. In addition the ability of PTH to increase renal 1-alpha-hydroxylase activity diminishes with age and may contribute to the age associated increase in PTH. Depending on the 25-OH D status and renal function, final 1-25 dihydroxyvitamin D will or will not be normal. Consistent with this some studies have not reported lower serum 1-25 dihydroxyvitamin D levels in elderly whereas others have.

1.6.8 Calcium

The concentration of calcium in plasma is maintained within a very narrow range, despite the large movements of calcium across gut, bone, kidney and other tissues. The major hormones involved in calcium homeostasis are 1-25 dihydroxyvitamin D and parathyroid hormone. These hormones regulate the ionised fraction of plasma calcium by modulating calcium fluxes to and from the extracellular fluid. The principle effects of 1-25 dihydroxyvitamin D on calcium metabolism are to increase intestinal absorption of calcium and phosphate. Because of the age-related decrease in calcium absorption and in renal calcium conservation, elderly people have an increased requirement of dietary calcium. On the contrary, evidence from studies, suggests that the proportion of elderly people ingesting less than two-thirds of the recommended daily allowance (RDA) of calcium is in the range of 19-40% for males and from 35-43% for elderly females. Thus, current calcium intake is inadequate in a large number of the older population- the groups at most risk of osteoporosis. When the amount of calcium absorbed from the diet is insufficient, calcium must be withdrawn from the bone, which contains 99% of total body stores of calcium. However, most elderly subjects fail to increase their calcium intake to offset this age related increase in calcium requirement.

The evidence relating dietary calcium to osteoporosis is conflicting (Cumming *et al*, 1990). Most research has focused on the relationship of calcium intake to *bone density* rather than fracture. Only a weak relationship has been observed between self reported calcium intake and bone mass or bone loss in cross sectional studies (Cummings *et al*, 1990; Nordin and Heaney, 1990). In epidemiological studies including 48 healthy men aged 21-79 years,

dietary calcium intake was a significant independent predictor of BMD of axial bones (Kelly *et al*, 1990). Diet calcium explained 24-42% of the variance at the lumbar spine and femoral neck BMD, respectively. In contrast, BMD at the forearm was not predicted by diet calcium. A more consistent relationship has emerged from calcium supplementation trials, which generally have shown a small, but positive effect of calcium on bone (Dawson Hughes *et al*, 1997).

Fewer studies have examined the relationship between dietary calcium and hip *fracture risk* and these have also produced conflicting results. Most of the studies have been case-control designs. In a case control study including 300 elderly men and women with hip fracture and 600 matched controls, a decrease in hip fracture risk in men with a calcium intake above 1g was observed (Cooper *et al*, 1988). The 5 prospective trials looking at the role of calcium in hip fracture risk have not ended the confusion. A subsequent cohort study by the same group with, 15 year follow up of 1688 British elderly people including 720 men aged 65 and over, to determine whether dietary calcium intake was a risk factor for hip fracture, did not reveal any relationship between the two in either sex (Wickham *et al*, 1989). Some prospective studies (Holbrook *et al*, 1988; Looker *et al*, 1993) found a protective effect of calcium on hip fracture, while others (Wickham *et al*, 1989; Paganini-Hill *et al*, 1991; Meyer *et al*, 1997; Owusu *et al*, 1997) found no effect between calcium and hip fracture in men. A calcium intake of more than 765 mg per day was associated with a 60% lower rate of hip fracture in men (and women) compared to those with an intake below 470 mg (Holbrook *et al*, 1988). In contrast, low dietary calcium intake was not a risk factor for hip fracture in another study (Wickham *et al*, 1989). Differences may have stemmed from the way the dietary calcium intake was collected, i.e. the abbreviated food frequency questionnaire using six foods to assess calcium intake (Paganini-Hill *et al*, 1991), single 24 hour recall (Holbrook *et al*, 1988; Looker *et al*, 1993; Meyer *et al*, 1997) and the 7 day food record (Wickham *et al*, 1989). Some of the studies were not powered (Holbrook *et al*, 1988; Wickham *et al*, 1989) with small number of fractures (n=33 and 44 respectively). The other two studies (Paganini-Hill *et al*, 1991; Meyers *et al*, 1997) were better powered with 418 and 213 hip fracture cases respectively. However, they failed to show any protective effect of calcium on hip fracture. This could be accounted for by the very low calcium intake from

food in their samples: median and upper tertile were 371 and > 501 mg/day respectively. Large variation in the quantity of calcium intake from food in the various studies may also explain discordance between study results. The most recent study exclusively addressing this issue in men is the Health Professionals Follow-up Study (Owusu *et al*, 1997). Among 43,063 men aged 40-75 years followed for 8 years, 56 hip fractures were recorded. After controlling for age, smoking, BMI, physical activity, alcohol consumption and total energy intake the relative risk for hip fracture for men in the highest quintile of calcium intake compared to the lowest quintile was 1.19; similarly relative risk for consuming >600 ml milk per day compared with 240 ml or less per week was 0.97. This large study of healthy men did not support a relation between calcium intake and incidence of hip fracture in men.

1.7 BONEMARKERS

1.7.1 Background

Osteoporosis is a disease characterised by a low bone mass and by microarchitectural deterioration of bone tissue related to abnormalities of bone turnover. Bone turnover is characterised by two opposite activities; the formation of new bone by osteoblasts and the resorption of old bone by osteoclasts. Both the activities are tightly coupled in a sequence of events. Bone mass depends on a balance between the two within a remodelling unit and on the number of remodelling units that are activated within a given period of time in a defined area of bone. Osteoporosis is characterised by both an imbalance between the two processes within a remodelling unit, and by an increased activation frequency, the latter being responsible for increased bone turnover after menopause.

Invasive procedures for measuring bone turnover have provided useful information but have limitations. They are less accurate for assessing bone resorption although they provide unique information on the rate of formation at both the cell and the tissue levels and allow estimation of activation frequency of remodelling units. Calcium kinetic studies and the use of labelled bisphosphonates have not proven to be sensitive. These limitations, in addition to the need for non-invasive techniques that can be applied more widely and repeated several times in an individual, explain the development of markers of bone turnover to be measured in blood and urine.

Osteoporosis is a condition where subtle modifications of the bone-remodelling unit can lead to a substantial loss of bone turnover over time. This explains why results with most conventional markers are normal despite established osteoporosis in the individual. This explains the continued efforts to develop more sensitive biochemical markers of bone turnover.

The rate of bone formation and resorption can be studied either by measuring an enzymatic activity of the bone forming or resorbing cells or by measuring the bone matrix components released into the circulation during formation and resorption. Although grouped into markers of bone formation and those of resorption, in disease states where both events are

coupled and occur in the same direction, any markers will reflect the overall rate of bone turnover. They cannot discriminate between turnover at cortical versus cancellous bone sites but reflect whole body net changes.

The markers are of unequal specificity and sensitivity, which implies that estimating the net excess of one over the other, will result in wrong conclusions. These markers are also influenced by factors other than bone turnover, such as their metabolic clearance. Hence, validation of each marker in specific disease states is important before concluding its clinical utility.

1.7.2 Biochemical markers of bone formation

Bone formation markers include total (TALP) and bone specific alkaline phosphatase (BALP), osteocalcin (OC) and carboxyterminal (PICP) and aminoterminal propeptide (PINP) of type I procollagen.

Alkaline phosphatase: Bone specific alkaline phosphatase appears to be more sensitive than TALP for clinical purposes. A significant increase in BALP after menopause is noted, significantly higher than TALP and decrease following treatment with bisphosphonate is larger for BALP than for TALP (Adachi *et al,* 1996)

Osteocalcin: Osteocalcin is a vitamin D dependent protein that has been estimated to represent upto 20% of all non-collagenous protein in bone. It is only found in bone tissue and dentin. A proportion of newly synthesised OC is released into circulation, where it can be measured by immunoassay. Thus, the serum level of osteocalcin is a very specific marker for the rate of bone formation. When resorption and formation are coupled, serum osteocalcin levels reflect bone turnover.

Procollagen type I extension peptides: More than 90% of the organic matrix of bone consists of type I collagen with the non-collagenous proteins comprising the remaining 10%. Type I collagen is synthesized as procollagen precursor molecules. Before inserting into the extracellular matrix, the terminal propeptide extensions are proteolytically removed. Thus both the PICP and PINP propeptide of typeI procollagen are released into circulation. There is evidence that both PICP and PINP assays are measures of bone formation.

1.7.3 Biochemical markers of bone resorption

Fasting hydroxyproline and urine calcium corrected for creatinine are measures of bone resorption that have been employed for many years. Newer resorption markers include tartrate-resistant acid phosphatase, galactosyl hydroxylysine, urinary pyridinoline (Pyr), deoxypyridinoline (Dpyr), N telopeptide of type I collagen (NTx) and carboxyterminal telopeptide of type I collagen (ICTP) and urinary cross-laps.

Plasma tartrate-resistant acid phosphatase: Osteoclast contain a tartrate –resistant acid phosphatase that is released into circulation. The lack of specificity of plasma tartrate-resistant acid phosphatase, its instability in frozen samples, and the presence of enzyme inhibitors in serum limits its clinical usefulness.

Galactosyl hydroxylysine: Hydroxylysine is an amino acid that is involved in collagen metabolism. Galactosyl hydroxylysine is five or six-fold more concentrated in typeI bone collagen than in skin collagen. At present, it is not suitable for routine measurements because it is a technically complex and demanding assay.

Pyridinoline and Deoxypyridinoline: Pyr and Dpyr are two nonreducible trivalent cross-links that stabilise the typeI collagen chains and are released during the degradation of mature collagen fibrils. Pyr is abundant in bone and cartilage, whereas Dpyr is largely, although not entirely, confined to bone. It is possible to measure only free fractions of Pyr. During bone resorption, only about 40% of the crosslinks are released in free form. The remaining 60% remain peptide bound.

N and C carboxyterminal telopeptides of typeI collagen: It has been established that typeI collagen has two cross-link-forming sites: one in the amino terminal peptide region and one in the carboxyterminal region of the molecules. Two immunoassays to detect NTx and ICTP have been described.

Crosslaps: Urinary excretion of cross-laps is determined by an immunoassay that recognises a small aminoacid sequence of ICTP. It correlates closely with total excretion of Pyr measured by high-pressure liquid chromatography (HPLC). The cross laps assay do not cross react with either free Pyr or free Dpyr.

Urinary hydroxyproline: Hydroxyproline results from the degradation of various forms of collagen. Because only half the collagen in the human body is found in the bone, urinary hydroxyproline is in part dependent on other sources and diet. After active liver metabolism, free and peptide bound urinary hydroxyproline represents only a fraction of total collagen catabolism and correlate poorly with histomorphometry.

1.7.4 Bone markers in men

There have been important developments in the field of bone markers in women in the last few years looking at their usefulness in daily clinical practice. Researchers have addressed effects of treatment (hormones, bisphosphonates) on bone markers (Prestwood *et al*, 1994), whether determination of biochemical markers of bone turnover is useful to monitor skeletal effects of hormone replacement therapy (Riis *et al*, 1995), whether they would be useful to predict future bone mass (Hansen *et al*, 1991) and changes in bone markers in patients with vertebral osteoporosis (Delmas *et al*, 1993) and following hip fracture (Akesson *et al*, 1993, 1995). In summary, studies have demonstrated excellent correlation between predicted and measured bone mass measurements for groups of patients: however their predictive value in individuals is not as good. Most studies conclude that biochemical markers of bone turnover are beneficial as early indicators of response to therapy. Establishing a relationship between bone markers and fracture prediction is still in its infancy.

Whereas in women several potentially important factors have been identified, the pathology of age-related bone loss in men is not known. It still remains unclear if similar age related changes in bone metabolism as in women occur in males. The usefulness of bone markers in men is less well studied.

1.7.5 Effect of age and sex

Almost all studies have shown a good correlation between the markers (r=0.35 to 0.77) (Gallagher *et al*, 1998; Kenny *et al*, 1998). Only one study has examined differences in bone markers between the genders (Gallagher *et al*, 1998). The study demonstrated that both mean osteocalcin and mean 24 hour urine N telopeptide were significantly lower (13 & 30% respectively) in men compared to women. However, the effect of age on bone resorption

and bone formation in men is still controversial. Some studies report a decrease in bone formation (Wishart *et al,* 1995; Clarke *et al,* 1996) and bone resorption (Wishart *et al,* 1995), some an increase in bone formation (Orwoll *et al,* 1990) and bone resorption (Clarke *et al,* 1996) while others no relationship of bone turnover with age (Resch *et al,* 1994). Discrepancies between results in literature can be explained in part by different radioimmunosystems or differences in the populations studied as shown below.

The influence of sex and age on bone markers was studied in 155 healthy subjects including 64 men (Resch *et al,* 1994). The study suggested different age-related alterations in bone metabolism in males and females. Contrary to evidence of increased bone turnover in females, bone markers remained unchanged in healthy males above or below the age of 50years, indicating no relationship between bone turnover and age. Another study looked at bone turnover along with bone mineral density and sex hormones in a group of healthy community living men (n=35) but aged over 75 years (Kenny *et al,* 1998). Deoxypyridinoline levels were above the normal range for premenopausal women in 23% men. This was in line with the observations in a subset of 11 men over the age of 70 by Wishart and colleagues (1995). Both N telopeptide and C telopeptide were within the normal range while mean bone specific alkaline phosphatase was below the normal range for men. Similar age - related changes in osteocalcin and urine N telopeptide have been studied in 735 normal elderly Caucasians that included 235 men (Gallagher *et al,* 1998). Significant correlation's between age and serum osteocalcin (r=0.15) and 24 hour urine N telopeptide (r=0.23) were reported in their subset of men. An earlier study, in contrast, on a population highly selected for their health, failed to demonstrate any associations between age and bone markers (Sherman *et al,* 1992). A more recent study determined the effects of ageing on bone turnover in 178 healthy Caucasian men over a wider age range (20-79 years). The study showed that bone turnover is highest in the third decade, lowest in the fifth and sixth decade, with a small increase in some markers in the eighth decade (Fatayerji and Eastell, 1999).

1.7.6 Relationship between bone turnover and BMD

A variety of biochemical indicators have been related to bone loss in healthy men, including increases in urinary calcium, osteocalcin, serum parathyroid hormone and vitamin D levels (Sherman *et al*, 1992). In men with osteoporosis, urinary calcium and hydroxyproline excretion and serum alkaline phosphatase levels are increased, indicating increased bone turnover (Resch *et al*, 1992). Serum osteocalcin levels are also increased and vitamin D levels reduced, indicating increased bone formation (Demiaux *et al*, 1992).

A cross sectional analysis addressing the associations between bone turnover markers (osteocalcin and N telopeptide cross links), bone density and age was carried out in a group of 1087 healthy adults including 273 men aged 65-87 years (Krall *et al*, 1997). Serum osteocalcin and urinary NTx levels were each inversely related to BMD in men; however, the associations with spine BMD tended to be consistently weaker than with other skeletal sites. Subsequently, another study addressed the same relationship but exclusively in men over age 75 years (Kenny *et al*, 1998). This study showed that bone resorption markers correlated inversely with BMD of the whole body, femur and spine. However, markers of bone formation did not significantly correlate with bone density with the exception of an inverse correlation between osteocalcin and femoral neck BMD. This supported an earlier study showing a significant relationship between lower femoral neck BMD and higher serum osteocalcin levels in men (Sherman *et al*, 1992). This study also showed an inverse relationship between urine calcium/ creatinine and femoral neck BMD. Others (Kelly *et al*, 1990; Wishart *et al*, 1995) have not shown an association between bone markers, BMD and age. The only consistent finding in various studies seems to be the inverse relationship between serum osteocalcin and BMD. The strength of the inverse relationship between the two is similar (Krall *et al*, 1997; Sherman *et al*, 1992). It has therefore been suggested that serum osteocalcin may be an indicator of bone status at most skeletal sites (Krall *et al*, 1997). An explanation for the associations between markers and BMD to be weaker at the spine than other skeletal sites supports the assumption that non-bone, calcified soft tissue is detected in spine scans resulting in erroneous results.

Krall *et al* further analysed the relationship between bone markers and BMD at all sites. They showed the differences in mean femoral neck BMD between men with osteocalcin

values in the lowest quartile and those in the highest quartile was 8%. The corresponding differences between quartiles of NTx distribution were 7%. When examined by joint contributions of both markers (NTx and OC), the differences in femoral BMD between low and high groups increased to11%. Differences in BMD at the other regions of the hip, whole body and spine between extreme categories of both markers were also within the range of 8-16% (Krall *et al,* 1997). In summary, in most studies bone resorption markers along with serum osteocalcin bear an inverse relationship to BMD most consistently at the femur.

1.7.7 Correlation of bone markers to fracture risk

There is growing evidence that subjects with high levels of bone turnover are at greater risk for developing osteoporotic fractures. This suggests that biochemical markers of bone metabolism could be of value in risk assessment and clinical management of osteoporosis. However, clinical usefulness may be limited if there is marked variation within individuals over time, preventing reliable classification into high or low bone turnover states.

Bone resorption marker (NTx) was longitudinally evaluated over a 2-year period in a cohort of community dwelling elderly subjects aged over 60years (Bollen *et al,* 1997). This included 57 men. The study showed a relatively stable excretion of NTx over 2 years, good reproducibility and supported the use of markers in stratifying subjects according to level of bone resorption. This would help identify subjects with high turnover who may be at greater risk of fracture. However, there still remains the need to establish the actual level associated with increased risk of fracture.

Retrospective studies comparing bone marker levels in patients who had sustained an osteoporotic fracture and in controls are inadequate to assess the relationship between bone turnover and fracture. Indeed, bone turnover can change after fracture because of immobilisation, because of the callus formation and / or because of a frequent regional activation of bone turnover. Relating bone marker levels measured before fracture to subsequent risk of fracture is the only valid methodology to assess their clinical utility. Due to the heterogeneity in the pathogenesis and, potentially, in underlying bone turnover abnormalities, the predictive value of bone markers should be analysed separately for all types of osteoporotic fractures.

Bone turnover has been studied after hip fracture in a large group of females. The study showed increased urinary cross-links excretion and decreased serum osteocalcin levels compared to age-matched healthy elderly controls (Akesson *et al,* 1993). The authors suggested this increased bone resorption and decreased bone formation might be important determinants of low bone mass that characterise patients with hip fracture. Despite the importance of hip fracture in men as a major health problem, there are no published studies exclusively addressing this issue in men.

1.7.8 Bone markers to monitor therapy

Unlike studies in women examining whether determination of biochemical markers of bone turnover may be useful in monitoring skeletal effects of hormone replacement therapy, there is little published literature available looking at the effects of bone markers following treatment with bisphosphonates or testosterone replacement therapy. An uncontrolled study of testosterone treatment in 21 eugonadal men with vertebral osteoporosis showed a significant increase in spine bone density of 5% in six months, although no change in hip bone density was seen (Anderson *et al*, 1997). Subsequent analysis of the markers of bone turnover showed a reduction in bone resorption with testosterone.

Because of the small change in BMD (as compared to its long-term precision error) in patients treated with anti-resorptive drugs, monitoring treatment efficacy with only a bone mass measurement could at the earliest be performed 1 year-preferably 2 years- after therapy. Conversely, placebo controlled studies in women have shown a rapid decrease in levels of bone markers with treatment. This short-term decrease has been shown to correlate with long term increase in bone mass. Although bone markers cannot predict the absolute bone mass gain, measurement of markers before and after therapy is likely to provide similar but earlier evidence of drug effectiveness than bone mass measurement. The responsiveness of bone markers to treatment offers the possibility of early monitoring of drug efficacy in osteoporosis.

There are a number of limitations with the use of bone markers and explain to some extent the limited number of studies in men. Circulating and urinary bone markers reflect the overall level of bone turnover of the entire skeleton and do not allow discrimination between

trabecular and cortical bone. Different markers perhaps reflect different events of bone metabolism, and using a panel of markers is likely to provide more information on the complex aspects of bone formation and resorption. Since the abnormalities leading to bone loss is quite subtle in osteoporosis conventional markers are insensitive to change. Some of the newer markers still need to be further characterised, especially in terms of clearance and metabolism.

For clinical purposes, in patients with clearly low bone mass, the biochemical variables may not be that useful as risk predictors since it would generally be advised to treat these individuals regardless of their projected bone loss rates. In contrast, combinations of biochemical variables might be more useful in a group of patients with intermediate bone mass values in whom treatment decisions might be affected by knowledge that the rate of bone loss would be relatively high over the upcoming years. Furthermore, responsiveness of bone markers to therapy offers the possibility of early monitoring of the drug efficacy. The cost of a battery of markers, however, must be compared with the cost of serial bone densitometry. In clinical practice, combinations of biochemical indices can only partially, but not completely, replace serial bone density measurements.

1.8 Outcome: Mortality And Morbidity

1.8.1 Background

Fractures of the proximal femur (hip) represent the most serious complication of osteoporosis in terms of morbidity, mortality, disability and medical costs (Melton *et al*, 1993). The consequences are often calculated on economic costs. However, the human costs of osteoporosis include diminution in functional status, health status, and independence. From the individuals' perspective, quality of life is threatened by these declines; from a societal point of view, loss of functional independence is a major determinant of the need for home assistance and for permanent institutionalisation.

In 1990, about 30% of 1.66 million hip fractures world-wide occurred in men (Cooper *et al*, 1992). Due to the exponential rise in the number of hip fractures with age, the projected increase in the year 2025 will be 3.94 million (1.16 million men and 6.26 million women) increasing further by the year 2050 to 6.26 million (1.79 M men and 4.47 M women). Despite their growing importance, there is little published data addressing mortality following hip fracture in men and factors that may influence the outcome.

Contrary to the wealth of information on women with this problem there are only two studies assessing mortality and its determinants in men with hip fractures. Both studies (Poor *et al*, 1995; Diamond *et al*, 1997) are population based retrospective chart reviews from medical records and include 131 and 51 men respectively. The former (Poor *et al*, 1995) used data collected from medical records of all men aged 35 years and over in Rochester Minnesota who presented with a hip fracture between 1978-89. The authors assessed mortality at 30 days, 1 year, 5 years and 10 years and analysed determinants of reduced survival. The latter (Diamond *et al*, 1997) was a retrospective audit from medical notes of all men aged 60 years and over who presented with a hip fracture between 1 January and 31 December 1995 to St. George Hospital, Sydney. The authors assessed prognostic factors and outcome at 6 and 12 months post fracture. In addition, they compared the results to an equal number of women (n = 51) of similar age with the condition.

Most of the published work on mortality following hip fracture have either included very few men (Thorngren *et al,* 1993; Stavrou *et al,* 1997) or despite substantial numbers of men with hip fracture (> 100 men) have failed to analyse mortality and risk factors for poor survival by gender (Beals *et al,* 1972; Colbort and O' Muircheartaigh 1976; Jensen *et al,* 1979; Jensen *et al,* 1984; Magaziner *et al,* 1989; Parker *et al,* 1991; Nettleman *et al,* 1996; Wolinsky *et al,* 1997). The only studies with substantial numbers of men with hip fracture that have analysed mortality rates separately by sex (Myers *et al,* 1991; Sernbo *et al,* 1993; Aharonoff *et al,* 1997; Forsen *et al,* 1999) have again failed to analyse potential risk factors by gender. A common limitation of most studies is that they do not differentiate the mortality experience of individuals residing in nursing homes or other long -term care institutions at the time of fracture from that of community dwelling patients. Some restrict studies to select population groups who are ambulatory, home dwelling and cognitively intact (Aharonoff *et al,* 1997). Numerous studies include hip fracture cases younger than 55 years (Beals *et al,* 1972; Jensen *et al,* 1984; Poor *et al,* 1995) for whom the cause of fracture is severe trauma and for whom the prognosis of recovery is generally excellent. Moreover, except for the study by Poor and colleagues (Poor *et al,* 1995) most studies have restricted their analysis to studying the effects of some but not all risk factors in their patient cohort. Differences in age, sex, race, residence, ambulatory status and degree of co-morbidities makes comparisons across studies difficult. With these constraints in mind, from the existing literature, the following conclusions can be drawn.

1.8.2 Mortality rate

Reported rates of mortality in men with hip fracture vary from 11% (Lu-Yao *et al,* 1994) to 71% (Poor *et al,* 1995). A good deal of this variance can be explained by differences in method of case selection and characteristics of the study population - age, health status, cognitive status, ambulatory status, institutionalised patients or from a general population mix of the elderly, influence of major trauma, coexisting illnesses, variation in length of hospitalisation and most importantly time of assessment (early versus late mortality). A number of study designs have been used. Mortality in hip fracture patients has been compared with mortality in sex and age matched controls (Jensen *et al,* 1979; Poor *et al,* 1995; Browner *et al,* 1996), and with expected mortality in the general population

(Magaziner *et al,* 1989; Fisher *et al,* 1991; Pitto 1994; Cooper *et al,* 1997; Katelaris *et al,* 1996; Forsen *et al,* 1999). The following section summarises mortality rates following hip fracture at various time intervals. Where data by sex was available the mortality figures for men have been cited separately.

In hospital mortality rate: 2.0% - Ceder *et al,* 1980; 4.3% - Magaziner *et al,* 1989; 5.8% - Jensen *et al,* 1979

30 day mortality: 6.3% - Fisher *et al,* 1991; Men 11% Women - 6% Lu-Yao *et al,* 1994); Men 14% Women 6% - Diamond *et al,* 1997; 18.5% - Riska *et al,* 1970

3 month mortality: 8.2% - Magaziner *et al,* 1989; 13% - Lu-Yao *et al,* 1994; 12.5% - Fisher *et al,* 1991; Men 21.5% Women 15.2% - Jensen *et al,* 1979;

6 month mortality: 11.1% - Jensen *et al,* 1979; 12.6% - Magaziner *et al,* 1989; 18% - Marottoli *et al,* 1994; 20% - Kreutzfeldt *et al,* 1984; Men 20% - Diamond *et al,* 1997; Men 25% Women 20% - Jensen *et al,* 1979

12 month mortality: Men 16% Women 14% - Kenzora *et al,* 1984; 17.4% - Magaziner *et al,* 1989; 20% - Wolinsky *et al,* 1997; Men 20.7% Women 10.7% - Aharonoff *et al,* 1997; 23.7% - Fisher *et al,* 1991; 24% - Lu-Yao *et al,* 1994; Men 37.1% - Parker *et al,* 1991; Men 35% Women 21% - Schurch *et al,* 1996; Men 34% - Sernbo *et al,* 1993; Men 42% - Poor *et al,* 1995; Men 51.4% Women 33% - Gordon *et al,* 1971; Men 37% Women 23% - Miller *et al,* 1978; 50% - Beals *et al,* 1972; 27% - Jensen *et al,* 1979

2 years: Men 51.4% Women 37.3% - Gordon *et al,* 1971

3 years: 35% - Jensen *et al,* 1982; 43% - Jensen *et al,* 1979

5 years: 56% - Jensen *et al,* 1979; 84% - Beals *et al,* 1972; Men 60% - Poor *et al,* 1995

10 years: 90% - Beals *et al,* 1992; Men 71% - Poor *et al,* 1995

An attempt has been made to quantify the excess mortality, though the data for men with hip fracture is scarce. Most studies have consistently shown the excess mortality to persist for the first 4-6 months post fracture, although the precise figures vary. Excess mortality was

most apparent in the first 4 months following fracture, but persisted for at least 8 months (Miller *et al,* 1978). This was similar to the findings by Gordon and colleagues in 1971 who noted the period of greatest mortality within 12 weeks of fracture (Gordon *et al,* 1971). In contrast, Jensen and co-workers found that the survival rate did not parallel the expected rate until 1.6 years after the fracture (Jensen *et al*, 1979). Others (Evans *et al*, 1979) found in addition to an early period of high risk of death, a secondary rise occurring after 4-6 weeks. The only study comparing the excess mortality by sex (Forsen *et al,* 1999) concluded that the excess mortality is short term (up-to 3 months) in women and longer (up-to 1 year after the hip fracture) in men.

The most detailed analysis of mortality amongst men with hip fractures comes from the recent population-based, prospective, matched-pair, cohort study in the county of Nord-Trondelag (Forsen *et al,* 1999). The study comprises of 1338 women and 487 men with a hip fracture along with 11086 women and 8141 men as controls. The study showed that men have a higher mortality than women irrespective of age after a hip fracture. The excess mortality is seen up-to 3 months in women but longer (up-to 1 year after fracture) in men. Amongst younger patients (<75 years) in the first 3 months after hip fracture men had a 9 fold increased risk of dying compared to a 5 fold increased risk in women. This risk changed to 5-fold in men and 6-fold in women in the age group 75-84. Among cases 85 years or older the excess mortality in the first 3 months was 6 fold in men and 4 fold in women.

1.8.3 Factors associated with mortality

In women, factors that have been shown to influence mortality after hip fracture include type of fracture, age and sex of the patient, presence of co-morbidity, cognitive state, place of residence, peri-operative factors and post operative complications. Contrary to the wealth of literature available addressing the outcome following a hip fracture in women and factors that determine it, there are only two studies exclusively addressing this issue in men (Poor *et al,* 1995; Diamond *et al,* 1997). Poor and colleagues using a population based cohort study design involving 131 men and an equal number of age-matched controls from the community addressed the issue of determinants of reduced survival following hip fracture in men. Risk factors for early death were age, male sex, post-operative deterioration in mental status, nursing home residence prior to fracture, functional limitation before fracture and

presence of co-morbid diseases. Type of fracture and nature of surgery were not risk factors. On similar lines, Diamond and co-workers retrospectively audited medical records of all men and women (n=51 each) aged 60 years and over a one year period. They analysed mortality and risk factors for death in men and compared the results to those found in women. Compared to women, men in their study had a higher prevalence of excess alcohol consumption, pre-existing medical illness and fracture related complications. Despite this, in men, age, smoking history, alcohol intake, pre-existing medical illness, pre-fracture Barthel index score and length of hospitalisation did not contribute to fracture related mortality.

Most of the published work addressing outcome and determinants of survival after hip fracture have predominantly included women and have generalised the results to either sex. Studies with significant number of men have either not performed separate analysis by gender (Aharonoff *et al,* 1997; Myers *et al,* 1991) have limited their observations in men to one or more risk factor only [Jacobsen *et al,* 1992 (race and sex); Forsen *et al,* 1999 (age and sex)] or addressed factors associated with short term (in-hospital) but not long term mortality (Myers *et al,* 1991).

The following section summarises the current data on potential risk factors for mortality following fracture. Most of the results come from studies in which the predominant population studied is women. Where separate analysis for men was available the data has been cited.

Age: Most studies have found that advancing age is associated with increased mortality after hip fracture (Gordon *et al,* 1971; Beals *et al,* 1972; Miller *et al,* 1978; Dahl *et al,* 1980; Magaziner *et al,* 1990; Myers *et al,* 1991; Fisher *et al,* 1991; Sernbo *et al,* 1993; Poor *et al,* 1995; Schurch *et al,* 1996; Stavrou *et al,* 1997; Aharonoff *et al,* 1997). Some have found no relation between age and mortality (Kenzora *et al,* 1984; Mossey *et al,* 1989; Diamond *et al,* 1997). The only two studies that have addressed this issue in men provide conflicting results: no association (Diamond *et al,* 1997*)* versus a 1.4 fold increase in death associated per decade increase in age (Poor *et al,* 1995). The small sample size of the former with few deaths may be one explanation for the conflicting results.

Sex: The relationship between gender and risk of death after hip fracture remains controversial. Gender was not predictive of increased mortality in some (Kenzora *et al,* 1984; Jensen *et al,* 1984; Aharonoff *et al,* 1997) but a risk factor for death in other studies (Gordon *et al,* 1971; Miller *et al,* 1978; Jensen *et al,* 1979; Dahl *et al,* 1980; Magaziner *et al,* 1989; Kellie *et al,* 1990; Myers *et al,* 1991; Fisher *et al,* 1991; Jacobsen *et al,* 1992; Sernbo *et al,* 1993; Poor *et al,* 1995; Schurch *et al,* 1996; Forsen *et al,* 1999). The number of studies addressing this issue are limited in the number of men included. The few studies with substantial numbers (Myers *et al,* 1991; Jacobsen *et al,* 1992; Sernbo *et al,* 1993; Forsen *et al,* 1999) consistently show male sex associated with higher mortality than women. A comparative study addressing both race and gender in over 712027 subjects with hip fracture has shown that irrespective of race men have the highest mortality after hip fracture (Jacobsen *et al,* 1992). In a more recent study (Forsen *et al,* 1999) male hip fracture patients had higher mortality than women the first year after the injury, irrespective of age, both in absolute terms (31% and 17% respectively) and relative to age-matched controls). The study by Poor and colleagues also showed male sex as a risk factor for hip fracture.

Race: Most workers agree that Black race is associated with higher mortality following hip fracture. The earliest report (Myers *et al,* 1991) showed little differences in mortality by race (RR 1.1 for Whites versus Blacks). The large study (Jacobsen *et al,* 1992) specifically addressing this issue in 712027 hip fracture covered by the Medicare programme over 3 years reported that Blacks have a higher mortality after hip fracture compared to Whites. A more recent publication (Lu-Yao *et al,* 1994) similarly confirmed that Whites had the lowest overall post-fracture mortality of the racial groups studied. No differences were found in mortality between the races during the first 90 days post fracture; subsequent mortality was higher in Blacks RR = 1.2 (Lu-Yao *et al,* 1994). These finding were independent of type of fracture and treatment. A possible explanation for this observed difference was the lower socio-economic status and limited access to health care by the Black community.

Fracture type: There is considerable variation between reports evaluating mortality rates for extra and intracapsular fractures. This is probably caused by variation in types of patients treated, variable exclusion of some patients from the studies (example those with pathological or multiple fractures) and exclusion of younger patients.

Some early studies (Gordon *et al,* 1971; Beals *et al,* 1972) have noted a higher mortality rate for subjects with an intertrochanteric fracture, although more recent studies do not note any difference, particularly when accounting for age (Kenzora *et al,* 1984; White *et al,* 1987; Jensen *et al,* 1979; Dahl *et al,* 1980). Type of fracture was not predictive of increased mortality after hip fracture (Myers *et al,* 1991; Sernbo *et al,* 1993; Aharonoff *et al,* 1997; Koval *et al,* 1998). Using multiple logistic regression presence of cervical fracture increased the odds of death by 9.06 with fracture at femoral neck compared to that at the intertrochanteric site (Marottolli *et al,* 1994). The only study specifically addressing this issue in men (Poor *et al,* 1995) concludes that the type of fracture is not predictive of increased mortality after hip fracture.

Nature of operation: Some (Rodriguez *et al,* 1987; Broos *et al,* 1988; Skinner *et al,* 1989; Lu-Yao *et al,* 1994) but not all (Kenzora *et al,* 1984) studies have shown better survival following internal fixation compared to arthroplasty. These differences can be due to selection of healthier patients for internal fixation (Miller *et al,* 1978) with no significant relationship between duration of anaesthesia, blood loss, choice of fixative devise and outcome one year after hip fracture.

Co-morbidity: Hip fracture patients are almost all elderly and many are frail. Poor controlled systemic illnesses, such as cardiac failure, diabetes, chronic airway disease have all been shown to increase mortality rate after hip fracture. Most investigators have found co-morbidities as significant predictors of increased mortality after hip fracture (Kenzora *et al,* 1984; Magaziner *et al,* 1989; Fisher *et al,* 1991; Myers *et al,* 1991; Marottolli *et al,* 1994; Poor *et al,* 1995; Nettleman *et al,* 1996; Aharonoff *et al,* 1997; Stavrou *et al,* 1997). A diagnosis of CHF or angina was an independent predictor of 30-day mortality after hip fracture (Nettleman *et al,* 1996). This is consistent with other studies (Myers *et al,* 1991; Kenzora *et al,* 1984).

There were inconsistencies in the two studies addressing this in men. Pre-existing medical illness did not contribute significantly to the fracture related mortality within 6 months of fracture (Diamond *et al,* 1997). However, one has to remember that the study was limited with a small sample size (n=51 men). In the study by Poor and colleagues, the effect of individual co-morbid components was not significant in the multivariate model, but the

overall influence of co-morbidity remained significant among patients with hip fracture after adjusting for other predictors of death (hazards ratio 4.4). Overall, patients with hip fracture had a higher mean co-morbidity score (2.8) and among the components of the score significantly more dementia (38%) (Poor *et al,* 1995).

The cause of death of these patients also reflects the co-morbidities. In their cohort of 131 men with hip fracture, Poor and colleagues found the cause of death at 1 year were more likely to be gastrointestinal disease (SMR 3.8); malignancies (SMR 2.6); stroke (SMR 2.6) and coronary artery disease (SMR 1.7) (Poor *et al,* 1995). These findings were corroborated by Nettleman and co-workers a year later where the cause of death in their men were similar (Nettleman *et al,* 1996).

Residence: Relatively few studies have looked at the effect of pre-fracture residence on outcome. Living in nursing home increased the odds of death both in the short term (90 days-OR 1.39) and long term (up-to 3 years-OR 1.54) (Lu-Yao *et al,* 1994). Nursing home residence prior to fracture increased risk of mortality at 1 year especially in the younger age group (Fisher *et al,* 1991). Patients coming from institutions had a 3-4 times higher mortality rate than those coming from home (Holmberg *et al,* 1986). Of the two studies in men only the study by Poor addressed residence as a risk factor. Discharge to a nursing home predicted death in univariate analysis but pre-fracture residence in nursing home did not alter 30 day mortality (Poor *et al,* 1995. This may partly be due to the relatively small number of deaths.

Mental status: Cognitive disorders are good predictors of mortality. The role of pre-fracture mental status using formal assessment tools on outcome has not been studied to a large extent. Poor baseline mental status with more than four errors on the short portable mental status questionnaire was significantly associated with death after hip fracture (OR 6.92) (Marottolli *et al,* 1994). Some workers have studied presence of dementia on admission as a risk factor for poor outcome. Some (Magaziner *et al,* 1989) did not but others have found dementia or presence of organic brain syndrome highly predictive of death within one year of hip fracture (Beals *et al,* 1972; Miller *et al,* 1978). Differences may be explained by differences in inclusion of patients from extended care facilities with more

advanced dementia. Deterioration of mental status during hospitalisation was shown to be a risk factor by Poor with a hazards ratio of 9.2 (Poor *et al*, 1995). Similarly, cases with an ASA operative risk rating of 3 or 4 were more likely to die in the first year after hip fracture (Aharonoff *et al*, 1997).

Pre-fracture physical function: Very few studies have examined the role of pre-fracture functional status to mortality in men. Most studies in women have identified physical function before fracture as an important determinant of outcome. Subjects who were relatively immobilised "dependent" owing to illness prior to fracture were more likely to die at 1 year than those "independent" (Gordon *et al*, 1971). Similarly, pre-fracture dependency in basic activities of daily living (BADLs) predicted increased mortality one year post fracture (Aharonoff *et al*, 1997). Walking ability before fracture was an important factor in discriminating those who were going to die within 1 year and those who were able to return to their own homes 1 year after the fracture (Sernbo *et al*, 1993).

The results in the two studies in men are conflicting. Poor found activity status at the time of fracture a predictor of survival. Survival was worse among patients with hip fracture and controls who were inactive before the index date in the nested case-control study. Compared with men who were active patients with hip fracture who had limited activity or who were more or less confined to bed had hazards ratio of 2.1 and 5.6 respectively (Poor *et al*, 1995). On the contrary, Diamond and co-workers did not find pre-fracture Barthel index contributing to mortality at 6 months (Diamond *et al*, 1997).

Postoperative complications: Mortality is increased by specific post-operative complications, including sepsis, dislocation or other failure of the prosthesis. Aharonoff reported a strong correlation between mortality at one year and the presence of one or more in-hospital postoperative complication. (Aharonoff *et al*, 1997). The only study addressing this in men found post operative confusion to be a risk factor (RR 8.1) for early mortality (Poor *et al*, 1995).

1.8.4 Morbidity

Functional competence in basic and intermediate activities of daily living and physical functioning is markedly diminished after hip fracture. Subjects who fracture their hips tend

to have other diseases and functional limitations prior to the occurrence of the fracture. Thus, the hip fracture is often not the sole factor leading to functional decline; rather it is probably the cumulative effect of the hip fracture in the setting of other co-morbidities and limitations that leads to a profound decrease in functional capability. Factors that predict better recovery after hip fracture in women are consistent with the concept that outcome of hip fracture depends largely on the prior condition of individuals who suffer the fractures. Recovery of pre-fracture health status and or return to living at home is more common amongst patients who are younger, in better general health, and not demented. There is very little information along these lines in men. There is no data on quality of life following fracture in men.

The two studies that have addressed morbidity in men (Poor *et al,* 1995; Diamond *et al,* 1997) are descriptive in nature. At 1 year, of the 76 Rochester patients that were alive, functional outcome at 1 year revealed recovery to pre-fracture level of functioning in 41%: 68.4% needed an aid to walk, 29% were bedfast or chair or bedridden and only 19.7% could walk independently. At 1 year 45% resided in a nursing home, 8% were in intermediate care facilities, 26% were at home requiring help with only 21% living independently in their own homes. No relationship was noticed between functional outcome parameters or nursing home placement and type of surgery, age, co-morbidity, presence of dementia or deterioration of mental status, attendance at nursing home or duration of physical medicine and rehabilitation (Poor *et al,* 1995). Functional outcome after 1 year was not studied. In the study by Diamond, of the 41 men who were contactable for assessment of outcomes at 6 and 12 months 50% were institutionalised and a significant (17%) decline in Barthel index score was observed amongst the survivors compared to pre-fracture scores. More detailed assessment was limited due to the small sample size.

1.8.5 Functional outcome and factors influencing it

A number of studies have looked at factors prior to fracture that may influence functional outcome in women. No such studies are available for men. The key predictors of functional outcome in studies in women are listed below.

Age: Advancing age (more than 85 years) has been shown to predict failure to recover basic activities of daily living after fracture (Koval *et al,* 1998; Magaziner *et al,* 1990; Mossey *et al,* 1989). Miller *et al,* 1978 also found that the probability of non-ambulation at one year after fracture increased markedly with age after the age of 60 years.

Sex: Patients gender had not been shown to be a significant predictor of functional outcome (Koval *et al,* 1998) nor have an effect on ambulatory status at 1 year (Miller *et al,* 1978).

Fracture Type: The role of fracture type in functional outcome rarely has been studied. Fracture type was not a predictor of functional recovery (Magaziner *et al,* 1990; Koval *et al,* 1998).

Pre-fracture functional status: A good score on basic activities of daily living (ADL) before fracture was strongly predictive of recovery post fracture at all assessment intervals (Koval *et al,* 1998)

Co-morbidity: Presence of one or more co-morbid condition was a predictor of failure to recover pre-fracture basic activities of ADL at 3 and 6 months (Koval *et al,* 1998), but not 12 months after fracture (Magaziner *et al,* 1990; Koval *et al,* 1998). This suggests that functional recovery is delayed in the presence of co-morbidities. The severity of co-morbidities was not a predictor of recovery of basic ADL.

Pre-fracture residence: Living alone before sustaining a fracture was a significant predictor of failure to recover basic ADL status at 3 months (Koval *et al,* 1998). This confirms earlier findings that social circumstances influence recovery (Cummings *et al,* 1988). Lack of social support at baseline has been reported to be an important predictor of institutionalisation (Ceder *et al,* 1980; Fitzgerald *et al,* 1988). Similarly, being married and a good pre-fracture mental status were protective against institutionalisation (Marottolli *et al,* 1994).

Despite the critical importance of hip fracture and the comprehensive literature available for women, to date, the current knowledge in relation to men remains inadequate. The lacuna lies in there being no prospective studies, limitations in using hospital discharge data taken from medical records including incompleteness and inaccuracy, no national studies, comparisons with inappropriate groups and most reports being descriptive as they have not

involved multivariate analysis. The need therefore is a comprehensive prospective study primarily targeted at assessing outcome following hip fracture in men with the aim of identifying treatable / modifiable factors associated with poor outcome. It must be remembered that neither acute nor long-term mortality rates after hip fracture are attributable solely to hip fracture, since they represent all-cause mortality estimates.

Hip fractures represent a significant source of morbidity and mortality for the elderly population. The number of hip fractures treated is rising throughout the world; nonetheless, outcome results remain poor. Comprehensive prospective studies are needed to guide surgeons to optimise patient survival and postoperative functional recovery. Many determinants of outcome are independent of the level of care given and are dependent on pre-fracture status. In today's cost cutting environment, caution must be taken to prevent short-term cost saving measures from compromising long-term outcome for elderly hip fracture patients. Particular attention is needed addressing the relationship between pre-fracture status and outcome.

2. SUBJECTS AND METHODS

2.1 Summary

This chapter describes the various methodologies used in this study. These include details about the method of recruitment, calculation of sample size, identification of the two study populations, questionnaires administered, laboratory tests, bone mineral density measurement and process involved in follow-up which implied contact with the vital registration system.

2.2 Study Setting

The study was undertaken at the Royal Cornwall Hospital in Truro. This is only centre for acute orthopaedic care in Cornwall and serves 80% of the total population (the other 20% of the population are seen in Plymouth and other hospitals in Devon). This provides a population base of 384,000 people (including 65,858 men aged over 50 years).

2.3 Study Design

This was a case control study. Both cases and controls were recruited simultaneously over a 14 month duration (December 1995-January 1997). The initial aim of the study was to assess the role of hypogonadism as a risk factor for low trauma hip fracture in elderly men. However, it was soon clear that it would be vital to re-assess hormone levels following fracture in addition to studying the role of many other potential risk factors. It was then decided to capitalise on the follow-up visits and address outcome following hip fracture both in terms of mortality and morbidity. As a result, both groups were prospectively followed for a mean of 661 days (1.8 years) (range 2-1128 days).

2.4 Sample Size

The sample size calculation was based on estimates of the prevalence of low testosterone (< 9.0 mg/dl) in a population with the age distribution for male low impact hip fractures. However, there are no published data on the prevalence of low testosterone in the normal elderly population although it is believed that testosterone levels decline with increasing age. The estimates used were a low estimate of prevalence of 15% and a high estimate of 25%. For the low estimate a sample size of 97 in each arm of the study would be needed to detect a relative risk associated with low testosterone of 2.75 (α= .05; 1-β = .90). A sample size

of 92 would detect a relative risk of 2.5 (α= .05; 1-β = .90) using the high estimate. Given these figures, it was decided that a sample size of 100 in each arm would give the study adequate power if low testosterone was to prove an important risk factor for low impact hip fracture. In the event, the relative risk associated with low testosterone in the study was 3.07 and the observed power of the study was .9859.

As part of the decision to extend the study to assess the sequelae of male hip fracture, the power of the sample to detect any associated risk of mortality was considered. Using Cornish age specific mortality figures for 1995 (ONS data) the "expected" one- (7.41%) and two- year (15.02%) mortality was estimated for the control group. Using those figures, the study would have been powered to detect (α= .05; 1-β = .92) a relative risk of mortality of 3 in the year following fracture and a relative risk of 2.5 over the two years following fracture (α= .05; 1-β = .93).

2.5 Subjects

2.5.1 Cases

Men aged 50 years or more, presenting with a low-trauma hip fracture and not having any malignancy requiring active treatment were eligible as cases. “Low - trauma” was defined as fall from standing height or less. 100 men consecutively presenting to the Royal Cornwall Hospital fulfilling these eligibility criteria were identified by checking the admissions register of the two orthopaedic wards on a daily basis.

2.5.2 Controls

Controls were recruited from the community. A local general practice surgery was identified as the representative of the catchment population. A list was drawn of subjects fulfilling the following entry criteria: males aged 50 years and over with no history of hip fracture. A past history of other fractures did not qualify as exclusion criteria. Using this criteria, 2000 men were eligible as controls. When a case was admitted to the hospital, in parallel an age-matched control was invited to take part from this list. The recruitment of controls was random and simultaneous to identification of a hip fracture case. To finally recruit 100 controls, 185 subjects were invited to take part from this list of eligible men giving a

participation rate of 54%. No subjects withdrew from the study after giving informed written consent.

2.6 Clinical Assessment

2.6.1.1 General Physical Examination

A standardised clinical assessment was carried in both groups at baseline, 6 months and 1 year. This included a detailed history and physical examination. Difficulty in getting fracture patients onto the scales in the immediate post-operative period meant that it was only possible to measure height (n=51) and weight (n=53) in just over half the cases within 7 days of the fracture. An attempt was made to measure the maximum possible number of subjects. This increased the final numbers where anthropometric measurements were possible within the first 3 months of the fracture to 74 and 85 respectively. Three controls could not have their heights and weights measured; one was a diabetic amputee.

2.6.1.2 Questionnaires

A single interviewer administered all questionnaires during the time of the first visit in the controls and within 48 hours in men with a hip fracture. All the questionnaires used in this study are attached in Appendix 2. It was not possible to gather complete information in some subjects due to their very ill health in the immediate post fracture period, hearing and visual impairment, poor mental status and co-morbid diseases. Missing data in these individuals were collected from the next of kin or carer. If there was a doubt on the credibility of the information being provided or where no close relative was identified the subject was excluded from that particular analysis. In subjects living in institutional care information obtained from the subject especially in relation to recent events, medications and co-morbid conditions was checked from their carer and or medical notes to ensure accuracy.

Standardised questionnaires were used. They were based on those used in the European Vertebral Osteoporosis Study (EVOS) and the Mediterranean Osteoporosis Study (MEDOS). The quality of life was assessed using the generic Short Form 36 (SF-36).

The socio-demographic questionnaire (Appendix 2.1) was based on the EVOS questionnaire. It was administered to collect personal details, socio-demographic data,

mental score using the mini-mental test, lifestyle data on risk factors for development of osteoporosis and fracture, past and / or family history of osteoporosis and minimal trauma fractures. In cases, two additional sections captured details of current fracture and circumstances around the incident event.

The medical questionnaire (Appendix 2.2) collected data on frequency and risk factors for falls, concomitant diseases and medications that may be risk factors for development of osteoporosis along with intake of bone protective medications.

The standardised Short form 36 (Appendix 2.3) was used as the "generic" health assessment questionnaire. In addition, a section of the MEDOS questionnaire was used to assess "specific" effects of hip fracture on daily functional abilities. Both these questionnaires ascertained health status 4 weeks prior to assessment date (which in cases was prior to fracture). This enabled us to collect information on the individuals' pre morbid general health status and specific functional limitations. Similarly, baseline pain assessment in cases implied levels of pain in the 4 weeks prior to the onset of their hip fracture.

2.7 Laboratory Assessment

2.7.1.1 Timing of samples

Baseline samples were collected at the time of the first visit in controls and within 48 hours of admission in men with a hip fracture. Subsequent samples were collected as per protocol at 6 and 12 months in both groups. All blood samples were collected early morning after an overnight fast to avoid potential diurnal variation. All urine specimens were 2 hour second morning urine samples following an overnight fast.

2.7.1.2 Handling and storage of samples

Blood and urine samples for routine tests were sent off for analysis immediately after collection and results were available in the majority within 48 hours. Blood samples for osteocalcin, 25-hydroxy-vitamin D, parathyroid hormone and free testosterone were centrifuged at 200g for 8 minutes to separate the serum. Serum thus obtained and urine for assay of deoxypyridinoline was split into 250 ul aliquots, snap frozen and stored at -70° C until assay. A strict cold chain was maintained during transportation of the samples between

storage site and laboratory to prevent thawing of the samples at a later date. All stored sera were analysed in one laboratory (Clinical Biochemistry, King's College, London) by trained staff. The assays were run in one analytical batch.

2.7.1.3 Details of tests

Routine haematological and biochemical tests were carried out in the Clinical Haematology and Biochemistry departments based at the Royal Cornwall Hospital. The aim of these was to exclude secondary causes for hip fracture. The assays were performed as per standard protocol.

Routine haematological and biochemical tests included full blood count (FBC), C reactive protein (CRP), plasma viscosity (PV), serum protein electrophoresis, bone profile (corrected calcium, alkaline phosphatase, total protein, albumin, globulin), renal function tests (B urea, S creatinine), thyroid function tests (TSH, thyroxin), prostate specific antigen and urine calcium creatinine ratio. Androgen status in both groups was evaluated using 3 assays: serum testosterone, free androgen index (FAI) which controls for sex hormone binding globulin (SHBG) and free testosterone. Levels of the two gonadotrophins, follicular stimulating hormone (FSH) and luteinising hormone (LH), were additionally analysed to fully characterise the androgen profile.

Tests carried out for research purpose:

Free testosterone radioimmunoassay: Free testosterone was measured using the DSL-4900 ACTIVE ^{TM} free testosterone coated-tube radioimmunoassay kit in accordance with the manufacturer's instructions for the standard method. This utilises an I ^{125}labelled testosterone analogue, which has low affinity for SHBG and albumin. The analogue competes with the unbound testosterone in the test sample for binding to specific anti-testosterone polyclonal antibodies that have been immobilised on the assay tube. This competitive binding format allows direct estimation of unlabelled free testosterone levels in unextracted samples. The procedure follows the basic principle of RIA where there is a competition between a radioactive and a non-radioactive antigen for a fixed number of antibody binding sites. The amount of I ^{125} labelled testosterone analogue bound to the antibody is inversely proportional to the concentration of the free testosterone present. The detection limit of this assay is 0.18 pg/ml. The mean intra-assay (n=10) CV over the range

of 1.87-28.53 pg/ml is 5.2-6.2%. The inter-assay (n=14) CV over the range of 3.7-34.02 pg/ml is 7.3 -9.7%. The assay cross-reactivity with dihydrotestosterone is <0.1%.

Oestradiol immunoassay: The Bayer Immuno1 system was used. This is a competitive immunoassay, where test samples are incubated with an antibody reagent to which an enzyme conjugate reagent is then added. The enzyme conjugate competes for binding sites with the oestradiol in the sample. The next step is the addition of the magnetic particle reagent to allow separation of the antigen-antibody complex. Excess reagent is then washed away and the enzyme substrate is added. The indicator reaction is the conversion of p-Nitrophenyl phosphate and water to p-Nitrophenoxide and phosphate that is catalysed by the alkaline phosphatase which forms part of the enzyme conjugate. This reaction is monitored at 405 nm. A sample having no oestradiol will have maximum label bound, while samples containing higher oestradiol concentrations will have less labelled bound. Hence the dose/response curve is inversely proportional to the concentration of oestradiol in the sample. The analytical range for this method extends from the minimum detectable concentration of oestradiol (10 pg/ml [36.7 pmol/l]) to 3600 pg/ml [13212 pmol/l]. The reference range for an adult male is <170 pmol/l. At this range between batch CV is 8.4% and within batch CV 1.8%. Cross reactivity with other naturally occurring steroids changed the oestradiol concentrations by <0.1%.

***25-hydroxyvitamin D radioimmunoassay*:** Quantitative determination of 25-hydroxyvitamin D was performed using a two-step assay. The first involved rapid extraction of 25-OH-D from the serum with acetonitrile. Following extraction the treated sample was then assayed using an equilibrium RIA procedure. The RIA method is based on an antibody with specificity to 25-OH-D. The sample, antibody and tracer are incubated for 90 minutes at 20-25 °C. Phase separation is accomplished after a 20-minute incubation at 20-25 °C with a second antibody-precipitating complex. The sensitivity of this assay is<3ng/ml. The coefficient of variation is less than 10%. The cross reactivity with Vitamin D2 and D3 is 0.8%.

***Intact PTH immunoradiometric assay (IRMA*):** Quantitative determination of intact parathyroid hormone in the serum was performed using Nichols Institute Diagnostics intact PTH immunoassay with a sensitivity of 1 pg/ml. This is highly specific for only biologically

active and intact PTH molecules. The intact PTH immunoassay is a two-site immunoradiometric assay (IRMA). Two different goat polyclonal antibodies to human PTH have been purified by affinity chromatography to be specific for well defined regions on the PTH molecule. One antibody is prepared to bind only the mid-region and C-terminal PTH 38-84 and is immobilised onto plastic beads. The other antibody is prepared to bind only the N-terminal PTH 1-34 and this antibody is radiolabeled for detection. The inter and intra assay (n=20) CVs over the range 38-277 pg/ml were <6.1 and <3.4 % respectively. Cross reactivity and interference with other PTH fragments is zero.

Patients' sample is incubated simultaneously with an antibody-coated bead and the ^{125} I labelled antibody. Intact PTH present in the sample is bound by both the immobilised and the labelled antibodies to form a "sandwich" complex: bead anti-PTH (39-84)- Intact PTH (1-84)- ^{125} I anti-PTH (1-34)

Although mid-region and C-terminal fragments are bound by the antibody coated bead, only the intact PTH 1-84 forms the sandwich complex. The bead is washed to remove the unbound components and the radioactivity bound to the solid phase is measured in a gamma counter-the radioactivity of the bead bound complex is directly proportional to the amount of intact PTH in the sample. A dose response curve of radioactivity vs. concentration is generated using results obtained from standards that are assayed concurrently with the unknowns. Concentrations of intact PTH are determined directly from this curve.

***Osteocalcin immunoassay*:** Intact osteocalcin in serum was assayed using NovoCalcin ™ kit as per manufacturer guidelines. The assay uses human osteocalcin coated strips and bovine- antiosteocalcin antibody with a high homology to human osteocalcin. There is 100% cross-reactivity recognising only intact osteocalcin, as it is "conformationally dependent". An anti-mouse alkaline phosphatase conjugate and anti-human parc nitro-phenol phosphate (pNPP) substrate are used to quantify osteocalcin. The assay has a minimum detection limit of 0. 45 ng/ml. The intra assay (n=22) and inter assay (n=3 in 3 runs) CVs over the range 6.2-16.5 ng/ml were <10 and <9.8% respectively.

Deoxypyridinoline immunoassay: Deoxypyridinoline cross-links were measured in the second morning void urine using the Pyrilinks-D immunoassay by Metra Biosystems. It is a

competitive enzyme immunoassay utilising a monoclonal anti-Dpd antibody coated on the microtitre strip wells. Dpd in the sample competes with conjugated Dpd-alkaline phosphatase for the antibody and the reaction is detected with pNPP substrate. Pyrilinks-D results are corrected for variations in the urine concentration by dividing the Dpd value (nmol/l) by the creatinine value (mmol/l) of each sample (creatinine mg/dl x 0.088 = mmol/l). The final results are expressed as nmol Dpd/mmol creatinine. The normal reference values of the assay for males aged 25 - 55 years is mean (SD) 3.8 (1.0); range 2.3 - 5.4. The within subject longitudinal variation of the assay is 15.5%. The monoclonal anti-Dpd antibody is selective and has a high affinity for free Dpd and negligible binding to Dpd peptides. The assay is sensitive to detect a minimum value of 1.1 nmol/l. The within and between-run CV of the assay at the range < 5.4 Dpd values is 8.4% and 4.8% respectively.

2.7.1.4 Algorithm for work-up of hypogonadism

Further investigation of individuals with abnormal endocrine results (low testosterone and or free androgen index) followed an algorithm that was designed to establish the type and nature of the hypogonadism: primary versus secondary. Dynamic pituitary function tests were not considered appropriate in these subjects because of their age. Patients with laboratory values consistently showing either normal testosterone (>9 ng/ml) and / or free androgen index (>30 IU/l) or a primary hypogonadal pattern (low testosterone (<9 ng/ml) / free androgen index (<30 IU/l) with raised LH (>10 IU/l) and or FSH (>10 IU/l)) did not have any further assessments. Subjects with low testosterone and low gonadotrophins (FSH & LH <10 IU/l) suggestive of secondary hypogonadism both at baseline and at 6 months were further investigated with measurement of thyroxin, cortisol and prolactin using serum stored from the two visits to identify the cause. Free thyroxin was performed only if total T4 was less than 70 nmol/l on both occasions. MRI / CT Scan of the pituitary was requested if prolactin values were over 2500 mIU/l on at least 2 occasions after excluding diseases or medications that may be responsible for these results.

2.8 Bone Mineral Density and Hip Axis Length Assessment

Bone mineral density (BMD) measurements were performed at the lumbar spine and proximal femur on all subjects capable of lying still in a specified position on the scanner for at least 10 minutes. BMD was measured by dual energy X-ray absorptiometry (DXA) using

Hologic QDR 1000. In the fracture cases, measurements were performed within 7 days of admission. The controls had proximal femur measurements made at the right hip, while in fracture cases the non-fractured side was assessed. Hip axis length (HAL) was recorded using the automated software provided with the scanner. The DXA unit is calibrated daily using the spine phantom provided by the manufacturer. The coefficient of variation in assessment of HAL and BMD in our unit is 0.4%. No significant change in the phantom's BMD value was noted during the study period. BMD was measured in all of the controls and 62 cases. The reasons for non-scanning among the cases include early death, extreme frailty and concurrent co-morbid diseases (36) and, refusal (2). In a further 4 cases measurements were not made at the proximal femur, because of prosthesis (2), frailty (1) or extreme obesity (1).

2.9 Ethics Approval

A patient information sheet was created outlining the objectives of the study, study duration and the proposed protocol. The hospitals' ethics committee approved this. This information sheet was provided to all eligible subjects at the time of recruitment into the study. Each study participant gave informed written consent before being enrolled into the study. For subjects with visual impairment the information sheet was read aloud. Similarly, for patients who were confused on admission consent was taken from the closest relative or carer.

2.10 Follow-up Assessment

Study subjects (cases and controls) were reviewed at 6 months, 12 months and 24 months (Table 2.1). In the majority, follow-up assessments were carried out in the hospital setting. In subjects who were in institutional care, very frail or had problems with transport follow-up visits were arranged at their place of residence.

General physical examination: This was carried out either in the hospital or in the subjects' own place of residence. An attempt to measure height and weight was restricted to the first 3 months following recruitment into the study.

Generic Quality of Life assessment: The SF-36 questionnaire was administered to both groups at the time of the follow-up visits at 6, 12 and 24 months. An additional "follow-up

questionnaire" (Appendix 2.4 & 2.6) captured data on current residence, outcome of surgery (in cases), current medications, occurrence of further fractures and degree and nature (i.e. family/ social/ paid help) of help needed to perform activities of daily living.

Specific Quality of Life assessment: The section of the MEDOS questionnaire (Appendix 2.3) was used at follow-up visits to assess the specific functional limitations of an individual in normal daily activities.

Laboratory assessment: Laboratory assessments were carried out using the same guidelines in both groups at 6 months and 1 year. The protocol is outlined in Table 2.1.

2.11 Outcome-Mortality and Cause of Death

Vital status of all study participants was collected at each assessment interval by direct contact with the patient, relative or carer. The cause of death was confirmed using death certificates or post-mortem reports obtained using the vital registration system from the registrar general office.

2.12 Statistical Analysis

The raw data was entered as a spreadsheet in EXCEL -97. The data was then transferred to SPSS version 7.5.1 and STATA 4.0 depending on the need for a particular statistical analysis. Details of the various statistical tests employed are described under the "methods" section of the individual "results" section.

Table 2.1 Schedule of patient visit and observations

Activity	Baseline	6M	12M	24M
Signed informed consent	X			
Clinical Assessments				
Physical Examination	X	X	X	X
Height, Weight, BMI	X			
Demographic data	X			
Risk factors for OP	X			
Risk factors for falls	X			
Co-morbidity data	X	X	X	X
Concomitant drugs	X	X	X	X
Circumstances around current fracture	X			
Details of fracture	X			
Functional status Assessments				
SF - 36 Questionnaire	X	X	X	X
Functional part of MEDOS Questionnaire	X	X	X	X
Laboratory Assessments				
Serum:				
Routine haematology [1]	X	X	X	
Routine chemistry screen [2]	X	X		
Extended blood chemistry [3]	X	X		
Androgen status [4]	X	X	X	
Oestradiol assay	X	X		
25-hydroxy-vitamin D assay	X	X		
Parathyroid assay	X	X		
Osteocalcin	X	X		
Pituitary function tests [5]	X	X		
Urine:				
Urine electrophoresis	X			
Urine Ca/Cr ratio	X	X		
Urine deoxypyridinoline	X	X		
Radiological Assessments				
X ray pelvis with both hips	X			
Femoral neck & lumbar spine BMD using DXA	X			
Others				
Residential status	X	X	X	X
Record of adverse events	X	X	X	X
Other co-morbidities	X	X	X	X
Additional fractures	X	X	X	X
Health service utilisation	X	X	X	X
Mortality	X	X	X	X

Routine haematology [1]: Haemoglobin, Full blood count, Plasma Viscosity, C Reactive protein,
Routine chemistry [2]: Liver functions (serum protein, albumin, globulin, alkaline phosphatase, alanine transaminase), renal functions (blood urea, s creatinine), bone profile (calcium, corrected calcium, and phosphorus)
Extended blood chemistry [3]: Serum electrophoresis, Thyroid, prostate specific antigen
Androgen status [4]: testosterone, free androgen index, free testosterone, sex hormone binding globulin, follicular stimulating hormone, and leutinising hormone
Pituitary function tests [5]: Free thyroxin, cortisol, prolactin, and MRI scan of the pituitary fossa

3. DESCRIPTIVE EPIDEMIOLOGY AND LIFESTYLE RISK FACTORS

3.1 SUMMARY

The aims of this chapter are to describe the characteristics of low trauma hip fracture in elderly men, to outline their associated sociodemographic and life style features and to identify variables that increase fracture risk.

100 men aged 50 years and over with a low trauma hip fracture were recruited prospectively over 14 months. Simultaneously 100 aged matched controls were randomly enrolled from the community. Interviewer assisted questionnaires collected data in both groups; in cases these were administered within 48 hours of fracture. Anthropometric measurements (height, weight) were carried out in both groups at baseline.

The mean age of men with a low trauma hip fracture was 79.9 years. Fifty-five fractures were cervical, 45 intertrochanteric with the majority (67) occurring indoors. Ninety-three fractures followed a fall, in 70 of whom the fall was on the same level. Ninety-five had surgical intervention of which the commonest procedure was a Dynamic Hip Screw or Thompson's hemiarthroplasty. Fracture cases were older, had lower BMI, poor mental scores, multiple co-morbid disorders such as Parkinson's disease, dementia, poor vision, stroke, restricted mobility, poor dietary milk intake in childhood and frequent falls. They were frequently single, living alone or in care.

Risk of hip fracture is greatest in the seventh and eighth decade of life. Presence of co-morbid diseases and some dietary and lifestyle characteristics further the risk of hip fracture in this group of elderly men. Early identification of those at "high risk", namely single men, living alone or in care, with multiple co-morbid conditions who are restricted in mobility and have a tendency to frequent falls would help target preventive measures. This may subsequently reduce the number of low trauma hip fractures in elderly men. Measures such as adequate calcium intake in childhood, regular physical activity throughout adult life and improvement of general health should reduce the burden of the problem.

The study is limited in evaluating age and race as risk factors for hip fracture in men.

3.2 BACKGROUND

This study was performed at The Royal Cornwall Hospital. This is the only referral centre for acute orthopaedic care to the local population, which is geographically well defined, relatively stable and socially homogeneous. It serves an estimated 80% of the population of 384,000 people that includes 65,858 men aged 50 years and over.

All patients following hip fracture require hospitalisation. The study capitalised on the ability to capture consecutive admissions from a geographically defined population over a defined period of time. To ensure homogeneity only those resident in Cornwall were included in the study. Only men aged 50 years and over were included in this study to allow comparison with the published literature. No upper age limit was set to avoid selection bias.

Controls were randomly drawn from the community to ensure similar exposure to potential risk factors. A single large general practice, representing the catchment population, was identified to help provide controls. Cases and controls were recruited simultaneously over a 14-month period. This avoids bias due to seasonal variation.

This chapter explores the demographic and lifestyle risk factors for low trauma hip fracture in this elderly male population. The results of the analysis are presented as follows:

i) Descriptive characteristics of the fracture population which includes sociodemographic profile, circumstances in which they fracture, operative interventions performed and differences between those who sustain a cervical fracture compared to an intertrochanteric fracture

ii) Comparison of demographic and lifestyle factors between hip fracture cases and age-matched community controls, and finally

iii) Calculation of age-adjusted odds ratios for risk of low trauma hip fracture associated with the variables that have been found to be significantly different between cases and controls.

3.3 METHODS

3.3.1 Study Design And Subjects

100 consecutive male admissions to the Royal Cornwall Hospital with a "low trauma" hip fracture aged 50 years and over were recruited as cases. "Low trauma" was defined as a fracture following a fall from standing height or less. Hip fractures following major trauma, those not residents in Cornwall and with active malignancy were excluded. Simultaneously, 100 age-matched controls were randomly recruited from a local general practice register. Data in both groups was collected over a 14-month period. Details are given in chapter 2.

3.3.2 Questionnaires

Interviewer assisted questionnaires were administered within 48 hours to fracture cases and at the time of the first visit to controls. Details of these are given in chapter 2 and the questionnaires themselves are attached in appendices 2. Questionnaires captured personal details, sociodemographic data, mental score, lifestyle risk factors for osteoporosis, family history of osteoporosis, risk factors for falls and list of concomitant diseases and medications. In cases, details of current fracture and circumstances around the incident event were also ascertained. Where questionnaires were incomplete due to lack of information from patient or carer, data was excluded from the analysis.

3.3.3 Analysis

All data was entered in EXCEL, then transferred to SPSS and STATA for statistical analysis. For categorical variables, percentages were calculated and significance estimated using Pearson chi -square. Due to significant difference in age between cases and controls, adjustment for age was made in calculating odds ratios using STATA.

3.4 RESULTS

100 cases (99 Caucasians and 1 Chinese) were seen over 14 months giving an annual incidence of 140/100,000/year for first low trauma hip fracture in males over 50 years. All 100 community controls were Caucasian.

3.4.1 Fracture Details

There was no side predilection: of the 100 fractures - 51 involved the right hip, 48 the left and one patient had bilateral hip fracture. Fifty-five involved the neck of femur (including subcapital) and 45 the intertrochanteric region. The majority (67%) fractured their hip indoor see Table 3.1.

Table 3.1 Fracture details

	Details	Number
Type of fracture	Cervical	55
	Intertrochanteric	45
Side of fracture	Right	51
	Left	48
	Bilateral	1
Site of fracture	Outdoors	31
	Indoors	67
	Unknown	2

Many of the fractures occurred in the morning 40 (41.2%); only 11 (11.3%) occurred during the night. Ninety-three (93.9%) fractures followed a fall, in 70 (73.7%) the fall was on the same level (Table 3.2). The commonest cause for the fall was tripping 46 (48.9%) with change of posture during transfers next 36 (38.2%); most frequently from a chair 7 (7.4%). However, many could not give a clear history of the fall, and the circumstances of the fracture remained uncertain in 5%. Eighty-five (91.4%) cases testified to good light conditions at the time of the fall. Seven cases sustained concomitant fractures at other sites at the time of the incident hip fracture.

Ninety-five cases had surgery. The two most common operative procedures performed to stabilise the fractured were Dynamic Hip Screw and Thompson's hemiarthroplasty. These accounted for 85% of the operations performed (Table 3.3). Five cases were not considered fit for surgery and died within the week following hospitalisation.

A significant number of fractures occurred in the winter months (Nov-Feb) despite lack of environmental factors locally that may predispose to them i.e. ice or snow (Figure 3.1).

Table 3.2 Circumstances around fracture event

Variable	*Number* responding*		Number (percent)
Time of fracture	***97***	Morning	26 (26.8)
		Midday	14 (14.4)
		Afternoon	23 (23.7)
		Evening	23 (23.7)
		Night	11 (11.3)
Light conditions	***93***	Light	85 (91.4)
		Dark	8 (8.6)
Following a fall	***93***	on same level	70 (73.7)
		different level	23 (23.4)

Number* = number of cases in whom data was available

Table 3.3 Operative procedures

Nature of operation (n=95)	**No (%)**
Dynamic Hip Screw	43 (44.1)
Thompson's hemiarthroplasty	39 (41.9)
Bipolar hemiarthroplasty	4 (4.3)
Nailing	1 (1.1)
Screws	8 (8.6)

Twenty-nine (29%) cases were living alone in their homes when the incident took place. Twenty-five (25%) were living in care (residential and nursing home) see Table 3.5. No significant differences were found in respect of age, body mass index, residence, level of physical activity, nature and site of fall when comparisons were made between cases with cervical fracture against those with an intertrochanteric hip fracture (data not shown).

Figure 3.1 Seasonal variation in fracture occurrence

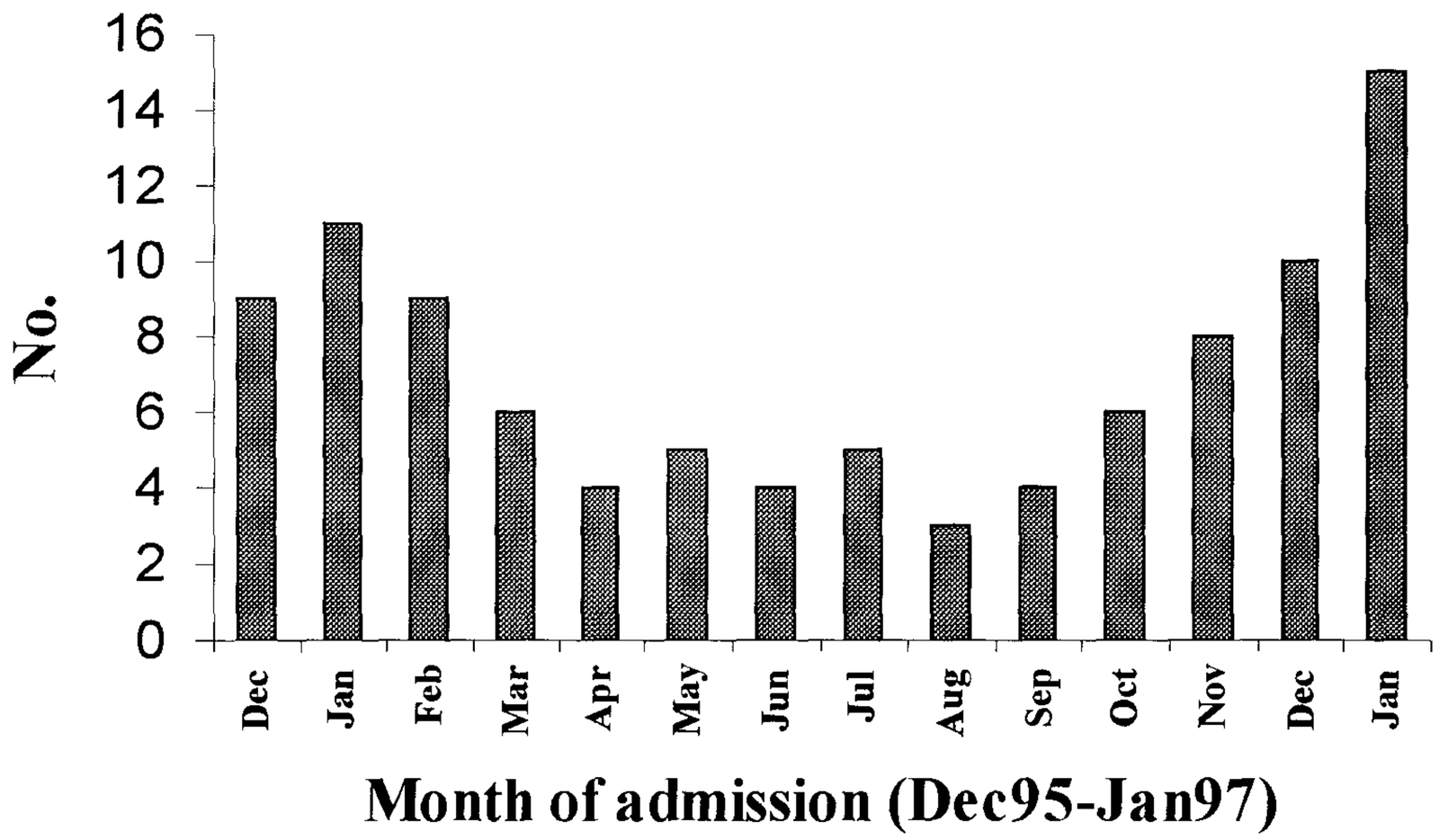


Table 3.4 Characteristics of hip fracture cases and controls

Variable	*No.*	Hip Fracture *Mean (SD)*	*No.*	Controls *Mean (SD)*	Significance
Age (yrs)	*100*	79.9 (9.4)	*100*	75.1 (9.6)	<.01
Height (cms)	*74*	170.6 (8.4)	*97*	170.6 (7.7)	NS
Weight (kg)	*85*	67.8 (11.2)	*97*	77.7 (16.3)	<.01
Body mass index (kg/m^2)	*72*	23.4 (3.3)	*97*	26.7 (5.5)	<.01

3.4.2 Age, Height, Weight And Body Mass Index In Cases And Controls

Cases were significantly older compared to controls ($p<0.01$) Table 3.4. These differences principally resulted from the difficulty faced in getting healthy elderly controls living in community to volunteer. However, the mean age per decade between cases and community controls was similar (data not shown).

Height and weight were recorded in 97 controls, and at or within 3 months of admission in 74 and 85 of the fracture cases respectively. Missing observations were a result of frailty, co- morbid conditions, death or difficulty in getting fracture patients onto the scale. Men with hip fracture were lighter (cases: mean 67.8 kg, SD 11.2; controls mean 77.7 kg, SD

16.3 $p<0.01$) and had lower body mass index (23.4 kg/m^2 Vs 26.7 kg/m^2 respectively) compared to controls. There was no difference in height.

3.4.3 Demographic Characteristics In Cases And Controls

Significant differences were noted in the marital and residential status between cases and controls. Cases more often lived in care or alone at home and were single 12 (12%) or widowed 30 (30%) at time of fracture compared to married controls 79 (79%) who were living with family in their own home Table 3.5. There was no significant difference in the type of area of residence (rural Vs. urban) either in childhood (rural 44.9% Vs 39%; urban 55.1% Vs 61%); adult life (rural 35.7% Vs 29%; urban 64.3% Vs 71%) or recent past (rural 45.9% Vs 33%; urban 54.1% Vs 67%) between cases and controls.

Table 3.5 Demographic details in cases and controls

Variable	***No***		**Cases**	**Controls**	**Significance**
Marital status	***100***	*Single*	12	3	$\chi^2=15.7$
		Married	55	79	df=4
		Divorced	2	-	$p<0.003$
		Separated	1	-	
		Widowed	30	18	
Residence	***100***	*Own home*	66	92	$\chi^2=24.5$
		Others home	4	4	df=5
		Residential H	14	2	$p<0.0002$
		Nursing H	11	2	
		Hospital	4	-	
		Others	1	-	
Living status	***100***	*Alone*	29	16	$\chi^2=15.7$
		With family	52	78	df=2
		With others	19	6	$p<0.0004$

Significantly more cases were fair complexioned than controls [91(93.8%) cases Vs 72(72.7%) controls, $\chi^2=15.6$, df=1, $p<0.001$] and tended to less often have brown or black

iris compared to controls [16(16.5%) cases Vs 30(30%) controls, χ^2=5.5, df=1, p<0.03). However, no difference in hair colour was noted.

Sixteen (16.3%) cases had difficulty in reading the newspaper which was explained by 6(6.1%) of the cases being blind and 10(10.2%) suffering from dementia or other conditions resulting in this handicap. None of the controls found this to be a problem and this difference was statistically significant χ^2=17.8, df=1, p<0.0001 Interestingly, all except 3-4% of subjects in both groups required the use of a visual aid/ spectacle.

3.4.4 Life Style Characteristics In Cases And Controls

There were significant differences in the main occupations of the two groups. The majority of cases (57/96, 58.4%) had been involved in manual work especially mining or agriculture. By contrast the majority of controls (53/100, 53%) had been office workers. This difference was highly significant (χ^2=15.6, df=4, p<0.004) as shown in Table 3.6.

Significant differences were also noted in the level of physical activity carried out by both groups during childhood and recent past. The majority of cases (52/91, 51.7%) had led a sedentary life in childhood compared to (32/100, 32%) controls (χ^2=13.6, df=3, p<0.004). Almost half 45(49.5%) the cases confirmed spending none to less than half an hour walking every day prior to fracture compared to less than a third 30(30%) controls (χ^2=11.8, df=3, p<0.008) However, there was no difference in the duration of previous prolonged immobilisation (defined as confinement to bed for a period of greater than 2 months) between the two groups.

Milk consumption in childhood, based on recall memory, was significant lower in cases compared to controls. "Adequate" milk was defined as intake of 1 pint per day or its equivalent. Milk intake in childhood was inadequate in (43/86, 50%) cases compared to (21/100, 21%) controls (χ^2=18.1, df=3 p<0.0004). In contrast, milk intake in adult life and in the recent past was similar in both groups. No differences were found in current dietary calcium intake between the two groups.

Table 3.6 Various lifestyle data: comparison between cases and controls

Variable		Cases (%)	Controls	Significance
Past occupation		***N=96***	***N=100***	
	Agriculture	21 (21.9)	7.0	χ^2=15.6
	Mining	36 (37.5)	30	df=4
	Office work	32 (33.3)	53	p<0.004
	Domestic	3 (3.1)	1	
	others	4 (4.2)	9	
Activity as child		***N=91***	***N=100***	
	Sedentary	52 (57.1)	32.0	χ^2=13.6
	Light	29 (31.9)	55.0	df=3
	Heavy	10 (11.0)	12.0	P<0.004
	Very Heavy	-	1.0	
Current walking		***N=91***	***N=100***	
	None	24 (26.4)	9	χ^2=11.8
	Less than ½ hr	21 (23.1)	21	df=3
	½ to 1 hr	22 (24.2)	29	P<0.008
	>1 hr	24 (26.4)	41	
Milk as a child		***N=86***	***N=100***	
	> 3 glasses /d	7 (8.1)	14	χ^2=18.1
	1-2 glasses /d	36 (41.9)	65	df=3
	Every week	17 (19.8)	11	p<0.0004
	Less than once /wk	26 (30.2)	10	

No differences in smoking habits were seen. Sixty nine (74.2%) cases and 70 (70%) controls had smoked sometime in life with 15 (16.1%) cases and 15 (15%) controls being current smokers (χ^2 =1.2, df=2, p=NS). In both groups more than 60% had been heavy smokers defined as having consumed more than 10 cigarettes per day at some time in their life.

Alcohol consumption was similar in the two groups. Twenty percent [18(19.6%) cases & 20(20%) controls] in both groups denied ever having alcohol with over 80% of "ever" drinkers denying history of "excess" intake (defined as intake of more than 21 units of alcohol per week). Approximately 60% [57(62%) cases and 60(60%) controls] of subjects in both groups were currently consuming alcohol in an acceptable amount.

3.4.5 Mental Status In Cases And Controls

Mini mental score examination in cases within 48 hours of fracture and in controls at first visit showed significant difference ($p<0.001$) between the two groups. Forty eight (52.7%) cases versus 84 (84%) controls scored 10 ($\chi 2=20.4$; df=1, $p<0.01$); 15 (16.5%) versus 3 (3%) respectively scored less than or equal to 5. Mental status could not be assessed in 9 cases due to severe dementia.

3.4.6 Past And Family History Of Fracture In Cases And Controls

History of any fracture following trivial trauma after the age of 40 years was recorded in order to see whether the subjects were accident-prone or showed signs of osteoporosis. History of previous fractures or family history of osteoporosis was not significantly different between the two groups (Table 3.7). Seventeen (17 %) cases and 12 (12%) controls gave a past history of a spontaneous fracture or following minor trauma (χ^2=2.7, df=2, p=NS). Three (3%) cases but none of the control had a documented vertebral fracture in the past.

Family history of fracture spontaneously or following minor trauma after age 40 years was seen in 5(5%) cases and 10(10%) controls. The most common relative to be affected was the mother and in the majority it involved the hip (Table 3.8).

Table 3.7 Past history of fracture after age 40 years following minimal trauma

	Level of trauma	No	Site of fracture					
			Hip	*Wrist*	*Humerus*	*Vertebrae*	*Others*	*Several sites*
Cases	*spontaneous*	**3**				2		1
	minor	**14**	3	1	1	1	4	4
Controls	*spontaneous*	**0**						
	minor	**12**		4	1		4	3

Table 3.8 Family history of fractures after age 40 years following minimal trauma

	Level of trauma	No	Relative with fracture				Site of fracture		
			Mother	*Sister*	*Father*	*Several Relatives*	*Hip*	*Wrist*	*Others*
Cases	*spontaneous*	1	1				1		
	minor	4	3	1			3		1
Controls	*spontaneous*	1	1					1	
	minor	9	6	1	1	1	5	1	3

3.4.7 Co-Morbid Diseases In Cases And Controls

Co-morbid diseases were present in the majority of cases and controls [79(82.3%) cases and 54(57.4%) controls; $\chi 2=13.8$; df=1, $p<0.001$]. Forty-seven (49%) cases had more than 2 pre-existing co-morbid conditions compared to only 18(19.1%) controls ($\chi^2=29.7$, df=7, $p<0.0001$). Cerebrovascular accidents, dementia, diseases affecting mobility like Parkinson's and poorer vision were significantly commoner in cases compared to controls ($p<0.001$). The most striking difference was in the number of subjects with dementia and Parkinson's;

26 and 14 versus 2 and 1 respectively in cases and controls. History of falls was significantly more frequent in cases compared to controls [35(36.5%) cases Vs 8 (8.4%) controls (χ^2=21.5, df=1, p<0.001)]. This could be explained by presence of co- morbid conditions like Parkinson's, poor vision, stroke, dementia and reduced mobility all of which were significantly commoner in the fracture cases than controls (Table 3.9). There was no significant difference in the frequency of heart disease (present in about 40% in both groups), thyroid disease, diabetes, osteoarthritis, malabsorption, gastro intestinal surgery, and dizzy spells between the two groups (data not shown).

Table 3.9 Co-morbid risk factors: Odds ratios (adjusted for age)

Co- morbid condition	**Cases**	**Controls**	**Odds ratio (95%CI)**
	No (%)	***No (%)***	***Adjusted for age***
Poor Vision	21 (21.9)	7 (7.4)	2.26 (0.86, 5.93)
Parkinson's	14 (14.6)	1 (1.1)	14.76 (1.89, 115.64)
Dementia	26 (27.1)	2 (2.1)	13.29 (3.01, 58.70)
Reduced mobility	25 (26.0)	4 (4.2)	8.36 (2.73, 25.60)
Falls	35 (36.5)	8 (8.4)	5.31 (2.27, 12.42)

3.4.8 Concomitant Medications In Cases And Controls

Use of medications was common in both groups. The most frequently used drugs were diuretics [29(30.2%) cases and 15(15.8%) controls; χ^2=5.6, df=1, p<0.02)] and hypnotics [10(10.4%) cases and 4(4.2%) controls; χ^2=2.7, df=1, p=NS)]. No significant differences were found in the frequency of intake of any particular medication that may be causally linked to the development of osteoporosis.

3.4.9 Age-Adjusted Odds Ratios For Demographic And Lifestyle Risk Factors

Odd ratios for risk of fracture associated with variables found significantly different between cases and controls were analysed using STATA. Correction for age difference between the groups was carried out using linear regression with age in the equation. Presence of co-morbid conditions increased the risk of hip fracture many fold: poor vision (OR 2.26; 95%CI 0.86, 5.93); reduced mobility (OR 8.36, 95%CI 2.73, 25.60) and dementia (OR 13.29; 95%CI 3.01, 58.7) Table 3.9.

With married as referent marital status, being single increased the risk of hip fracture almost seven fold (OR 6.83; 95%CI 1.76, 26.47) Table 3.10. Similarly, compared to living alone subjects living in care were at increased risk of hip fracture (OR 1.37; 95% CI 0.44, 4.25).

With no walking as referent a protective effect was noticed with increasing duration of walking: less than 30 minutes, 30-60 minutes and over 1 hour. The odds ratio were 0.37, 0.31, 0.26 respectively, with 95%CI ranging from 0.21 to 29.42. Similarly, milk intake in childhood and adult life was protective. With 3 glasses per day as referent the risk increased with reducing intake from 1-2 glasses per day to every week to less than once a week. The odds ratio were 1.94, 2.12 and 2.62 respectively with 95% CI ranging from 0.33 to 14.60.

Compared to never smokers, past versus current smokers were at increased risk of hip fracture (OR 1.35; 95%CI 0.54, 3.38 and OR1.77 95%CI 0.58, 5.45 respectively).

Table 3.10 Lifestyle risk factors: Odds Ratios (adjusted for age)

Variable	Categories	Odds ratio (age adjusted)
Marital status	*Married*	1.0
	Single	6.83 (1.76, 26.47)
	Divorced	-
	Separated	-
	Widowed	1.72 (0.84, 3.51)
Living	*Alone*	1.0
	With relatives	0.38 (0.18, 0.78)
	With others	1.37 (0.44, 4.25)
Residence on admission	*Home*	1.0
	Others home	1.11 (0.26, 4.80)
	Residential Home	7.56 (1.63, 34.98)
	Nursing Home	5.56 (1.16, 26.61)
	Hospital	-
Milk in childhood	*3 glasses per day*	1.0
	1-2 glasses per day	1.07 (0.39, 2.93)
	Every week	2.54 (0.76, 8.52)
	Less than weekly	4.3 (1.31, 14.12)
Walking in recent past	*None*	1.0
	Less than 30 mins	0.37 (0.14, 1.01)
	30-60 mins	0.31 (0.12, 0.82)
	More than 1 hour	0.26 (0.10, 0.66)
Smoking	*Never*	1.0
	In the past	1.35 (0.54, 3.38)
	Current	1.77 (0.58, 5.45)

3.5 CONCLUSION

Low trauma hip fracture in elderly males is common with an incidence of 140/100,000/year in Cornwall, which exceeds the only pre-existing UK incidence data on male hip fractures (114/100,000/year) from a 1985 study of 22 males in Oxford (Boyce and Vessey, 1985). The highest risk of hip fracture is in the seventh and eighth decade of life. They are commoner in the winter months, most occurring indoors after minor falls during change of posture or a result of tripping.

A number of sociodemographic and lifestyle variables are implicated in increasing fracture risk. These are being single (OR=6.8), living in care (nursing home OR=5.6; residential home OR=7.6), having low BMI (OR=4.2), along with multiple co-morbid conditions namely Parkinson's (OR=14.8), dementia (OR=13.3), reduced mobility (OR=8.4) and history of falls (OR=5.3). Regular walking (OR=0.26) and adequate intake of milk in childhood reduce the risk.

The study has limitations. Cause-effect relationship between variables identified and risk of hip fracture cannot be established due to the cross sectional design of the study. Matching the two groups for age prevented studying age as a risk factor for hip fracture. The geographic location of the study prevented evaluation of race as a risk factor.

Despite the above constraints and that the study was not strictly age matched it seems reasonable to conclude that simple measures like ensuring adequate calcium to children, encouraging regular walking in adult life, preventing falls and overall general improvement of health in the elderly men may reduce the burden of low trauma hip fractures. Preventive measures targeting the "high risk" individual namely single men, living alone or in care with low BMI, multiple co-morbid diseases and history of falls may reduce the number of hip fractures in this age group.

4. BONE MINERAL DENSITY: A RISK FACTOR FOR LOW TRAUMA HIP FRACTURE IN MEN

4.1 SUMMARY

This chapter explores bone mineral density (BMD) and its determinants in a community population of elderly men, compares these results with a matched hip fracture population and examines the role of BMD as a risk factor for low trauma hip fracture in men.

The populations studied (hip fracture cases and community controls) are those detailed in chapter 2. Sixty-two (62%) cases and all 100 controls underwent BMD measurement, at the lumbar spine and the proximal femur. BMD was measured by dual energy x-ray absorptiometry (DEXA). In fracture cases this was within one week of fracture and in controls at the time of their first visit. Interviewer assisted questionnaire collected data on lifestyle variables (appendices 2). Laboratory parameters were assessed as outlined in chapter 2.

A good correlation was seen between BMD at different sites in the control population. Mean BMD in community living men was 0.75g/cm^2 at the femoral neck and 1.08g/cm^2 at the lumbar spine. 39% of men aged over 50 years fulfilled the WHO criteria of osteoporosis at the femoral neck and 5% at the lumbar spine. BMD at the lumbar spine increased with advancing age; perhaps an effect of degenerative spinal disease. No significant age related changes were observed at the proximal femur. A significant positive relationship was seen between body mass index (BMI) and BMD at all sites; r_s =0.42; p<0.01 for lumbar spine and r_s =0.24; p<0.05 for femoral neck. Weight, physical activity like regular walking, past and family history of fracture together explained 20% of the variance in femoral neck BMD.

Cases had significantly lower BMD at all sites compared to controls: femoral neck (0.61g/cm^2 Vs 0.76g/cm^2 p<0.001) and lumbar spine (0.92g/cm^2 Vs 1.08g/cm^2 p<0.001). Cases were 7 times more likely to have osteoporosis at the femoral neck (OR 7.2, 95%CI 3.3, 15.9) and 10 fold more likely at the lumbar spine (OR 9.7, 95%CI 3.4, 27.8) compared to controls using WHO criteria. Using this definition low BMD increased the risk of hip fracture over 6 fold (Odds ratio (OR) 6.2-27.9 dependant upon the site measured).

This study shows that femoral neck BMD in the elderly men is influenced by BMI, physical activity, past and family history of fractures and levels of testosterone, oestrogen and urinary cross links but not significantly by age and calciotropic hormones. Low BMD is an

important risk factor for low trauma hip fracture in these elderly men. After adjusting for age, height and weight the risk of hip fracture is substantial per 0.1mg/cm^2 decrease in bone mass: lumbar spine - OR=1.2, 95% CI 1.0, 1.6; femoral neck - OR=2.0, 95% CI 1.3, 3.1.

4.2 BACKGROUND

The importance of low BMD as a risk factor for hip fracture is well established in women (Marshall *et al*, 1996). Each standard deviation reduction in bone mass increases the risk of hip fracture by a factor of 1.5-3 fold in women with the diseases (Marshall *et al*, 1996). Data for BMD in male hip fractures is sparse, yet one third of all hip fractures worldwide (Melton *et al*, 1998) occur in men. The data that does exists comprises of three small case-control (Karlsson *et al*, 1993; Greenspan *et al*, 1998; Boonen *et al*, 1997) and one population-based cohort study (Nguyen *et al*, 1996) of 820 men that included 31 hip fractures only. All found low BMD in hip fracture cases.

These studies have imitations. They include small numbers (ranging between 7 and 40 fractures), BMD measurements not contemporary to fracture and selection bias with exclusion of the very elderly and those in institutions. A study designed at capturing consecutive male hip fractures from a defined population and comparing data with controls randomly selected from the representative community would overcome these limitations. With this background this case control study measured BMD within one week of fracture and imposed no restrictions on age and place of residence.

This chapter explores BMD as a risk factor for low trauma hip fracture in men. In addition it analyses lifestyle and hormonal variables that may influence / determine BMD in men. The results of the analysis are presented as follows:

i) BMD and its determinants in community dwelling elderly men

ii) Comparison of BMD in men with a hip fracture versus men living in community

iii) BMD as a risk factor for low trauma hip fracture in men

4.3 PATIENTS AND METHODS

4.3.1 Study Design

100 consecutive men with low trauma hip fracture over a 14-month period were identified as cases. Simultaneously, an equal number of community living men were randomly recruited as controls. Details of study design, exclusion and inclusion criteria are given in chapter 2.

4.3.2 Bone Mineral Density Measurements

BMD was measured at both the lumbar spine and proximal femur by dual energy x-ray absorptiometry (DXA) using Hologic QDR 1000 on all subjects capable of lying still in a specified position on the scanner for at least 10 minutes. In cases this was within 7 days of the hip fracture and in controls at the time of their first visit. Controls had their right hip scanned; cases the non-fractured hip. The coefficient of variation in BMD in our unit is 0.40% calibrated daily using the spine phantom.

BMD was measured in all (100) controls and only 62 (62%) cases. In 4 of these 62 cases BMD measurements were possible at the lumbar spine but not at the femur. This was due to metal prosthesis in the non fractured hip following arthroplasty for osteoarthritis in 2 cases, inability to lie still on the scanner due to extreme frailty in 1 and difficulty in positioning due to extreme obesity requiring use of a hoist in 1 case. Early death, severe co-morbidity's, uncontrolled Parkinson's and extreme frailty explain why measurements were not performed in 36 cases. 2 patients refused scanning.

4.3.3 Anthropometry

Height and weight was measured in 97 controls at the time of their first visit. 2 controls were diabetic amputees and 1 very frail making measurements difficult. Height and weight was recorded at the time of admission or within subsequent 3 months in 74 and 85 fracture cases respectively. Missing observations were due to early death, extreme frailty and co-morbid conditions.

4.3.4 Endocrine Status And Bone Markers

Samples for assessing the endocrine status (androgen, oestrogen, vitamin D, parathyroid hormone) and bone markers (osteocalcin, urinary free deoxypyridinoline) were collected at

first visit and at 6 months in both groups. Details of the measurements performed, assays used and timing of the assays are presented in chapter 2. To explore the relationship between these laboratory parameters and BMD, baseline results amongst controls were used as they were contemporary to BMD measurements and not altered by the acute phase response following the fracture.

4.3.5 Lifestyle Questionnaire

Data on lifestyle variables was collected using an interviewer assisted questionnaire based on the EVOS (European Vertebral Osteoporosis Study) study forms which was administered at the time of initial assessment to both groups. The questionnaire is attached in appendix 2.

4.3.6 Analysis

All data was entered in EXCEL, then transferred to SPSS and STATA for statistical analysis. For categorical variables, percentages were calculated and significance tested using Pearson chi-square. Age adjustments were made in calculating odds ratios using STATA.

4.4 RESULTS

4.4.1 BMD In Community Controls

BMD was measured in all 100 controls. The mean age was 75.1 years (range 50-97); mean weight 77.7 kg (range 46.1-176.4) and mean body mass index 26.7 (range 18.5-66.2).

Mean BMD at the femoral neck was 0.76g/cm^2 and at the lumbar spine it was 1.08 g/cm^2 (Table 4.1). Using the WHO definition of osteoporosis (T score less than 2.5 SD of normal mean) 39% fulfilled the criteria of osteoporosis at the femoral neck and 5% at the lumbar spine. Twenty-nine of the 39 (74.3%) with WHO defined osteoporosis were over 70 years of age.

BMD at all sites correlated well with each other; Spearman's correlation (r_s) ranging between 0.50-0.83. Correlation between the lumbar spine and femoral neck was $r_s = 0.50$; $p<0.01$, $n = 100$.

4.4.1.1 Influence of age and BMI on bone density in community men:

Age showed no significant correlation with BMD at any site (Figure 4.1). A trend towards increasing BMD at the lumbar spine with advancing age was noted ($r_s = 0.15$; p = NS). This

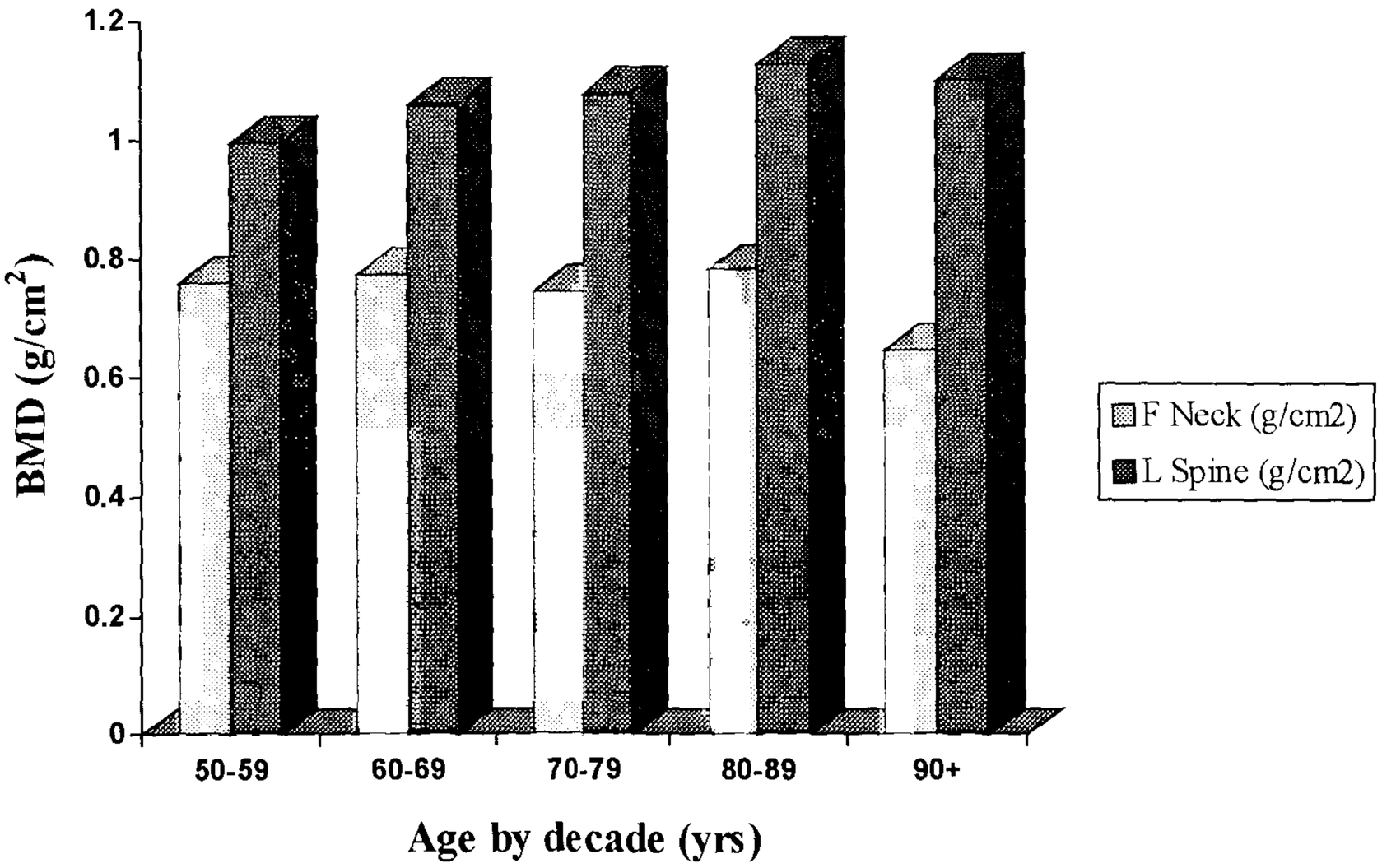
may be explained by coexisting degenerative spinal disease in the elderly. Age explained only 0.2% of the variance in femoral neck BMD ($r^2 = 0.002$) and 2% of lumbar spine BMD ($r^2=0.02$) using linear regression with the dependant variable being site specific BMD and independent variable age.

BMD correlated with BMI at both the lumbar spine ($r_s=0.42$; $p<0.01$) and the femoral neck ($r_s =0.24$; $p<0.05$).

Table 4.1 Subject characteristics and BMD (g/cm^2) in community controls

Variable	No	Mean (SD)
Age (yrs)	100	75.1 (9.6)
Weight (kg)	97	77.7 (16.3)
Body mass index (kg/m^2)	97	26.7 (5.5)
Lumbar spine (g/cm^2)	100	1.08 (0.20)
Femoral neck BMD (g/cm^2)	100	0.76 (0.13)
Intertrochanteric BMD (g/cm^2)	100	1.06 (0.16)
Trochanteric BMD (g/cm^2)	100	0.75 (0.13)
Wards Triangle BMD (g/cm^2)	100	0.52 (0.14)

Figure 4.1 Mean BMD (g/cm2) at the femoral neck and lumbar spine by decade



4.4.1.2 Influence of androgens, oestrogens, calciotropic hormones and bone markers:

BMD showed positive correlation with both sex hormones, testosterone and oestrogens. Androgens (testosterone, free androgen index, free testosterone) had a significant positive correlation with BMD at the femoral neck (r_s=0.25, n=97, p<0.01) but not at the lumbar spine. By contrast, oestrogen showed a significant correlation with BMD at both sites: femoral neck (r_s =0.25, n=98, p<0.01) and the lumbar spine (r_s =0.24, n=98, p<0.01). Using linear regression with dependant variable being site specific BMD and independent variable sex hormones (free androgen index and oestrogen) oestrogen seemed the more powerful determinant of BMD at either site. Individually they explained 6% (r^2=0.057) and 12% (r^2=0.12) of the variance in femoral neck BMD respectively. Multiple regression analysis was carried out with site specific BMD as the dependent variable and both free androgen index and oestrogen as predictors in the model. The analysis showed that both sex hormones played a role in determining BMD at the femoral neck but not at the lumbar spine (Table 4.2*)*. In combination they explained 17% of the variance in femoral neck BMD (r^2=0.17). Oestrogen alone accounted for only 0.6% (r^2=-0.006) variance in BMD at the lumbar spine.

Vitamin D and parathyroid hormone did not bear any relation to BMD at any site. Amongst the bone markers urinary free deoxypyridinoline exhibited a significant negative correlation with BMD at the femoral neck (r_s =-0.21, n=96, p<0.05) but not at the lumbar spine. Bone formation marker, osteocalcin, did not show any relation to BMD at any site.

Table 4.2 Multiple regression: Sex hormones as predictors of femoral neck BMD

Model	B	SE B	Beta	Sig
Constant	0.609	0.036		0.000
Oestradiol	0.0007	0.000	0.317	0.002
Free androgen index	0.001	0.001	0.194	0.05

4.4.1.3 Influence of anthropometric & lifestyle factors on bone density:

Variables known to influence BMD in women such as current height and body mass index, tobacco and alcohol intake, current dietary calcium, current walking, history of immobilisation, past and family history of fractures were initially considered for formulating

a regression model at each skeletal site. The variables included in the final model of BMD prediction was based on the results of a regression using backward elimination with the probability of "F" to eliminate set at >0.1 and "T" to include set at $p<0.05$. The regression analysis showed current weight, walking, past and family history of fracture as significant predictors of BMD at the femoral neck (Table 4.3). Together they explained about 20% of the variance in BMD at this site ($r^2=0.19$).

Predictors of BMD at the lumbar spine were different with the combination of BMI and calcium intake explaining 17% of the variance ($r^2=0.174$) see Table 4.4.

Table 4.3 Multiple regression: Predictors of femoral neck BMD

Model	B	SE B	Beta	Sig
Constant	0.56	0.08		0.0001
Current Weight	0.002	0.001	0.23	0.02
Walking	0.07	0.03	0.26	0.009
Past H of Fracture	-0.07	0.03	-0.25	0.01
Family H of Fracture	-0.07	0.04	-0.18	0.07

Table 4.4 Multiple regression: Predictors of lumbar spine BMD

Model	B	SE B	Beta	Sig
Constant	0.58	0.14		0.0001
Body mass index	0.02	0.005	0.332	0.001
Calcium	0.09	0.04	0.214	0.03

4.4.2 BMD In Fracture Cases

BMD was measured in 62 cases within one week of fracture. Early death, extreme frailty and co-morbid conditions like Parkinson's explain the missing observations in 36 cases. 2 cases refused scanning. Four of the 62 where BMD was measured could not have their hip scanned due to metal prosthesis in the non-fractured side in 2 cases, extreme frailty in 1 and obesity in 1 case.

Cases who could not be scanned (n=38) were significantly older (mean age 82.63 95% CI 80.34, 84.91) than those where measurements were performed (mean age 78.0 95%CI 75.41, 80.59; $p<0.01$). There was no significant difference in height, weight and body mass index between the two groups (data not shown).

The mean age of the 62 cases was 78.4 years (range 53.7-97); mean weight 67.6 kg (range 50.8-93.2) and mean body mass index 23.4 kg/m^2 (range 16.4-33.4). BMD at the femoral neck was 0.61gm/cm^2 (95% CI 0.59, 0.64); at the lumbar spine it was 0.92 gm/cm^2 (0.87, 0.97) see Table 4.5. Using the WHO definition of osteoporosis (T scores <-2.5), 83% (48/58) fracture cases had osteoporosis at the femoral neck and 36% (22/62) at the lumbar spine (Table 4.6). Thirty-eight of the 48 (79.1%) cases with osteoporosis were 70 years of age or older.

Table 4.5 BMD in fracture cases

Site		**BMD**		**Osteoporosis (T<-2.5)**	
	No	***Mean***	***SD***	***No***	***%***
Femoral neck (g/cm^2)	**58**	0.61	0.11	48	82.8
Trochanteric (g/cm^2)	**58**	0.58	0.13	22	37.9
Inter-trochanteric (g/cm^2)	**58**	0.82	0.14	35	60.3
Ward's triangle (g/cm^2)	**58**	0.38	0.11	52	91.2
Lumbar spine (g/cm^2)	**62**	0.92	0.20	22	36.1

Table 4.6 Percentage of cases & controls with osteoporosis at different sites: Using WHO definition T<-2.5

Site	**Osteoporosis (T<-2.5)**			
	Cases		***Controls***	
	no(%)		***no(%)***	
Femoral neck	48/58	82.8	39/100	39.0
Trochanteric	22/58	37.9	2/100	2.0
Inter-trochanteric	35/58	60.3	11/100	11.0
Ward's triangle	52/58	91.2	61/100	61.0
Lumbar spine	22/62	36.1	5/100	5.0

Relationship between BMD and age was analysed using linear regression with the dependant variable - site specific BMD and independent variable age. 12.8% of the variance in femoral neck BMD (r^2=0.128) and only 1.6% (r^2=0.16) of the variance in lumbar spine BMD could be accounted for by age. Since, all anthropometric recordings were not contemporary to BMD measurement, role of BMI in determining BMD in fracture cases was not explored.

Similarly, role of androgens, oestrogens, bone markers and calciotropic hormones in determining BMD in the fracture population was not analysed. Due to changes expected in the hormonal environment following a fracture, baseline samples were not considered appropriate to reflect the individuals' normal physiological state.

4.4.3 Comparison Of BMD Between Fracture Cases And Community Controls

BMD was measured at both the lumbar spine and proximal femur in 62 cases and all 100 controls. Bone mineral density was significantly lower in fracture cases than controls at all four sites of the proximal femur and at the lumbar spine - see Fig 4.2. At the femoral neck BMD was 0.61gm/cm^2 (95% CI 0.59, 0.64) in the fracture cases and 0.76 gm/cm^2 (0.73, 0.78) in the controls $p<0.001$. At the lumbar spine it was 0.92 gm/cm^2 (0.87, 0.97) and 1.08 gm/cm^2 (1.04, 1.12) respectively; $p<0.001$. These differences persisted after adjusting for age and body mass index (Table 4.7).

Figure 4.2 BMD in cases and controls

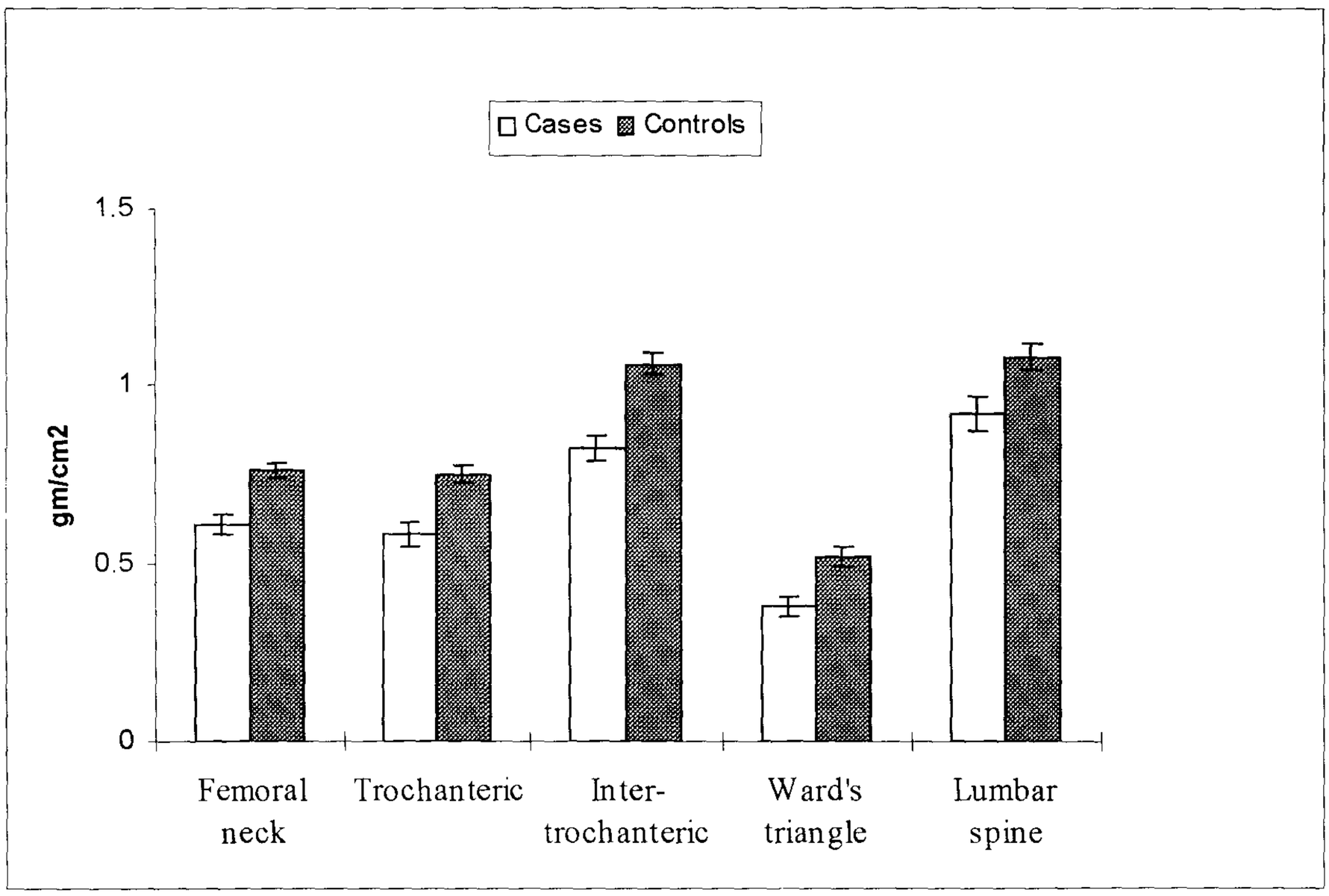


Table 4.7 BMD (g/cm^2) in cases and controls (mean, SD are shown)

Site	Cases n=62		Controls n=100		
	Mean	*SD*	*Mean*	*SD*	*t test**
Femoral neck (g/cm^2)	0.61	0.11	0.76	0.13	<0.01
Trochanteric (g/cm^2)	0.58	0.13	0.75	0.13	<0.01
Inter-trochanteric (g/cm^2)	0.82	0.14	1.06	0.16	<0.01
Ward's triangle (g/cm^2)	0.38	0.11	0.52	0.14	<0.01
Lumbar spine (g/cm^2)	0.92	0.20	1.08	0.20	<0.01

* significance level after adjusting for age, body mass index

Using the WHO definition of osteoporosis (T scores <-2.5), 83% (48/58) fracture cases had osteoporosis at the femoral neck compared with 39% (39/100) controls. At the lumbar spine 36% (22/62) cases had osteoporosis compared with 5% (5/100) controls. Thirty-eight of the 48 (79.1%) cases with osteoporosis were 70 years of age or older (Table 4.6).

Relationship between BMD and age was analysed using linear regression. The dependent variable was site specific BMD and the independent variable age. This showed that 12.8% of the variance in femoral neck BMD (r^2=0.128) in fracture cases but only 0.2% of the variance in controls was explained on the basis of age. Relationship between age and lumbar spine BMD in both groups was similar 1.6% (r^2=0.16) in cases and 2% (r^2=0.02) in controls.

4.4.4 BMD As A Risk Factor For Low Trauma Hip Fracture In Men

Bone density at the lumbar spine and all sites of the proximal femur was significantly lower in the fracture cases than in the controls. After adjusting for age, height and weight the risk of hip fracture increased substantially per 0.1mg/cm^2 decrease in bone mass: lumbar spine - OR=1.2, 95% CI 1.0, 1.6; femoral neck - OR=2.0, 95% CI 1.3, 3.1. Similarly, after adjusting for age, height and weight, the risk of hip fracture increased for each standard deviation reduction in bone mass at all sites measured: lumbar spine (OR=1.8), femoral neck (OR=3.1), trochanter (OR=3.9), inter-trochanteric area (OR=4.0) and wards triangle (OR=3.7) see Table 4.8.

Table 4.8 BMD in hip fracture cases and controls

BMD (g/cm^2)	Fracture *n=62*	Controls *n=100*	Sig♣	Odds Ratio/ 1 SD change$	
	Mean (SD)	**Mean (SD)**		**OR* (95% CI)**	**OR+ (95%CI)**
Lumbar Spine	0.92 (0.2)	1.08 (0.2)	<0.01	2.4 (1.6, 3.5)	1.8 (1.2, 2.9)
Femoral Neck	0.61 (0.1)	0.76 (0.1)	<0.01	4.2 (2.5, 7.1)	3.1 (1.8, 5.3)
Trochanteric	0.58 (0.13)	0.75 (0.13)	<0.01	4.1 (2.5, 6.6)	3.9 (2.2, 6.9)
Inter-trochanteric	0.82 (0.14)	1.06 (0.16)	<0.01	4.9 (2.9, 8.3)	4.0 (2.3, 7.1)
Ward's triangle	0.38 (0.11)	0.52 (0.14)	<0.01	4.5 (2.6, 8.0)	3.7 (2.0, 6.8)

♣ significance level; * adjusting for age; + adjusting for age, height, weight;

$ For BMD - per 1 standard deviation *decrease* in measurement

Using WHO definition (T score less than 2.5 SD of normal) the presence of osteoporosis at the femoral neck or the lumbar spine increased the risk of hip fracture 7-28 fold depending on the site measured (Table 4.9).

Table 4.9 Bone mineral density as risk factor for fracture

Site	Abnormal T score	Odds Ratio
Lumbar spine	<2.5	9.2 (3.2, 26.4)
Femoral neck	<2.5	6.9 (3.1, 15.3)
Trochanteric	<2.5	27.9 (6.1, 126.9)
Intertrochanteric	<2.5	13.2 (5.5, 31.5)
Ward's triangle	<2.5	6.2 (2.3, 16.9)

All odds ratios are adjusted for age. 95% confidence intervals are shown.

Among the 62 hip fracture cases with BMD measurements, there were 31 men with a cervical and 31 with an inter-trochanteric fracture. Compared to those with an inter-trochanteric fracture, those with a cervical fracture were slightly older (79.0 years Vs 77.0 years), taller (172 cms Vs 170.4 cms) and lighter (67.5kg Vs 67.8 kg) however, none of

these differences were statistically significant. Those with an inter-trochanteric fracture had lower BMD at all sites, though this was significant for the trochanteric region only, see Table 4.10. After adjusting for age, height and weight, the risk of inter-trochanteric (compared to cervical) fracture increased per standard deviation reduction in bone mass at the trochanteric region (OR=2.5; 95%CI 1.2, 5.4), see Table 4.10

Table 4.10 BMD in individuals with cervical and intertrochanteric fractures

BMD (g/cm^2)	Cervical (n=31)	Intertrochanteric (n=31)	Odds Ratio/ 1 SD change$	
	Mean (SD)	Mean (SD)	OR* (95%CI)	OR+ (95%CI)
Lumbar Spine	0.96 (0.20)	0.88 (0.19)	1.7 (1.0, 2.9)	1.5 (0.8, 3.1)
Femoral Neck	0.63 (0.11)	0.60 (0.11)	1.6 (0.8, 3.3)	1.7 (0.8, 3.7)
Trochanteric	0.63 (0.14)	0.53 (0.10) ♣	2.9 (1.4, 5.9)	2.5 (1.2, 5.4)
Inter-trochanteric	0.85 (0.14)	0.79 (0.14)	1.8 (0.9, 3.5)	1.6 (0.8, 3.2)
Ward's triangle	0.38 (0.10)	0.37 (0.11)	1.1 (0.6, 2.3)	1.4 (0.7, 3.2)

♣ significant $p<0.01$; * adjusting for age; + adjusting for age, height, weight;
$ Inter-trochanteric Vs cervical fracture; For BMD - per 1 standard deviation *decrease* in measurement

4.5 CONCLUSION

There is no existing criterion for diagnosing osteoporosis in men. Using the WHO definition for women, 39% of men living in community aged 50 years and over suffer with osteoporosis. Majority (74%) of these are very elderly (aged 70 years and over). Different lifestyle and laboratory variables influence BMD at various sites. While physical activity like regular walking, past and family history of fractures influences BMD at the femoral neck, calcium intake is important for lumbar spine bone density. BMI influences BMD at both sites. By contrast age has no correlation with BMD at any site in elderly men. Similarly, amongst the laboratory parameters androgens, oestrogens and bone resorption marker

urinary cross-links predict BMD at the femoral neck but not at the lumbar spine. The contribution of oestrogen is higher (12%) compared to testosterone (6%). Together they account for 17% of the variance in bone density at the femoral neck. In contrast, the role of bone formation marker osteocalcin and, calciotropic hormones vitamin D and parathyroid, in influencing BMD at any site is marginal/ insignificant.

Men with hip fracture are 7-10 times more likely to fulfil the WHO criteria for osteoporosis at any site compared to men living in community. This study was not designed to evaluate relationship between BMD and risk of hip fracture in men. The study has however shown that a reduction in BMD is associated with an increased risk of hip fracture in men. The associations are stronger for measurements at the proximal femur than the lumbar spine.

The magnitude of the risk of hip fracture associated with femoral neck BMD has been reported in several studies. Nguyen reported a 66% reduction in risk of hip fracture (n=31) per SD increase in BMD at the femoral neck (Nguyen *et al*, 1996), while De Laet (De Laet *et al*, 1998) reported a 3 fold increase in risk of fracture (n=23) associated per SD decrease in BMD. These data are similar to the findings of this study of a 3.1 fold increase in risk per SD decrease in femoral neck BMD.

The strength of the association between bone mass and fracture risk was greater for the measurements at the hip than those at the spine. This may be in part due to the presence of concurrent degenerative disease which leads to an artifactual increase in spinal bone density (Masud *et al*, 1993; Jones *et al*, 1996).

Bone mass, at all sites was lower in those with an inter-trochanteric compared to those with a cervical fractures, though the difference was significant for the trochanteric measurement site only. Similar findings have been reported using the Singh Index in men (Sernbo *et al*, 1989) and DEXA in women (Karlsson *et al*, 1993; Greenspan *et al*, 1994).

The study has limitations. It is using a cross sectional design to study the effects of age and other variables on BMD. Relationship between BMD and risk of fracture is explored applying the "WHO criteria for women" in "men", in the setting of a case control design. Recall bias cannot be excluded in collecting data on lifestyle variables dating back to childhood despite using standardised questionnaires in this elderly population. Also, the numbers of variables studied are large which may affect the power of the study to analyse

their individual effects on BMD and fracture risk. The constraints of using an anterior posterior view in measuring BMD at the lumbar spine using Hologic QDR1000 affecting measurements in the elderly due to degenerative spinal disease must not be forgotten.

Furthermore, fracture cases were recruited consecutively, and none invited declined to participate. Controls were recruited from a local general practice and a proportion (46%) declined. If this was because they were less healthy and therefore likely to have lower bone mass than those who took part, the observed differences in BMD between fracture cases and controls may have been overestimated.

The frailty and poor mobility of cases immediately after the hip fracture caused difficulties in obtaining data concerning bone mass in a significant proportion (38%). Individuals in whom BMD was not assessed were older and greater proportion had co-morbidities than those who were assessed-factors again likely to be linked with lower BMD. The effect of such a selection bias would be to underestimate the strength of the relationship between hip fracture and BMD.

In conclusion, a significant percentage (39%) of men living in community suffer with osteoporosis. Most of this is undiagnosed. Modification of lifestyle variables that influence bone density may help reduce the burden of the problem. Within the constraints of the study design low BMD is a significant risk factor for hip fracture in men. Studies are needed to establish a criterion for diagnosing osteoporosis in men and to quantify the risk of fracture associated. This will help in our understanding of this neglected problem in men and help plan measures to reduce the absolute number of hip fractures worldwide.

5. HIP AXIS LENGTH

5.1 SUMMARY

This chapter explores whether hip axis length (HAL) is a risk factor for low trauma hip fracture in elderly men.

Data on hip axis length was collected from the same subjects recruited in the case control study (described in chapter 2). Hip axis length was measured in all 100 controls and 58 of the 100 fracture cases. Hip axis length, defined as the linear distance from the base of the greater trochanter to the inner pelvic brim was measured using software provided with the scanner (Hologic QDR 1000). Measurements were performed at the same time as the bone mineral density estimates of the proximal femur. Controls had their right hip measured, cases the non-fractured hip. In cases this was within one week of the fracture and in controls at the time of their visit. Missing observations were a result of frailty, early death or co-morbid diseases making measurements impossible.

Men with hip fracture were older and had significantly lower body mass index. This was due to low weight rather than height. No differences were seen in hip axis length between the two groups (12 cms Vs 12.1 cms). HAL correlated with height (r_s=0.56, p<0.05) but not age. There was no relationship between HAL and the risk of hip fracture (Odds ratio [OR]=0.9 (95% CI 0.6, 1.3); this remained true after adjusting for height (OR=0.9 (95% CI 0.5, 1.5).

Results from this study suggest that assessment of hip axis length does not help predict risk of hip fracture in elderly Caucasian men. This study is limited by its cross sectional design. Prospective data are required to confirm these findings.

5.2 BACKGROUND

In the UK there are 70,000 low trauma hip fractures annually (Mc Coll *et al*, 1998) which cost the NHS 942 million pounds per year (Mc Coll *et al*, 1998). One third occur in men (Cooper *et al*, 1992). Identification of those at high risk of hip fracture would help target preventive therapy and reduce the health burden associated with these fractures. To date, bone mineral density is one of the best predictors of the risk of hip fracture in women and men (Marshall *et al*, 1996). The previous chapter (chapter 4) confirms low BMD to be a risk factor for hip fracture in our elderly community population.

Recent studies of risk factors for hip fractures in Caucasian women have suggested that factors other than BMD may be important in hip fracture prediction (Faulkner *et al*, 1993). Two measures of structural geometry of the proximal femur, namely hip axis length (HAL) and femoral neck axis length (FNAL), have recently drawn much attention (Peacock *et al*, 1995). In women, a 1SD increase in hip axis length (HAL) - the distance from the base of the greater trochanter to the inner pelvic rim along the femoral axis, is associated with a 1.8 fold increase in hip fracture risk (Faulkner *et al*, 1993). Femoral neck axis length (FNAL) where measurements exclude the acetabulum however, has not been shown to confer risk in either sex (Peacock *et al*, 1995), but the data in men is scanty (Center *et al*, 1998). There is no data on HAL in men.

The study capitalised on the ability to measure hip axis length using the automated method by use of a software specifically designed and compatible with the scanner simultaneous to BMD measurements of the proximal femur. All cases and controls that underwent BMD measurements at the proximal femur also had their hip axis length measured at the same time.

With this background, this chapter explores HAL as a risk factor for low trauma hip fracture in men in a case control setting.

5.3 METHOD

5.3.1 Study Design

This study used a case-control design with prospective and simultaneous recruitment of subjects in both groups over 14 months. They are the same subjects that are detailed in chapter 2.

5.3.2 Cases And Controls

100 consecutive male admissions to the Royal Cornwall Hospital with a "low trauma" hip fracture aged 50 years and over were recruited as cases. Simultaneously, 100 closest age-matched controls were randomly recruited from a local GP register. Full details are given in chapter 2. All subjects capable of lying still with their hip joint internally rotated and strapped in a specified position on the scanner (Hologic QDR1000) for at least 10 minutes

were consented for measurement of the HAL. This was performed simultaneous to BMD measurement at the proximal femur. Measurements were carried out within one week of the fracture in cases and at the time of the first visit in controls. 42 (42%) fracture cases could not have HAL measured. This was a result of extreme frailty, co-morbid conditions such as Parkinson's or death.

5.3.3 Hip Axis length Measurement

A software with the scanner (Hologic QDR 1000) specifically designed for this purpose was used to calculate the distance between the base of the greater trochanter and inner pelvic brim in centimeters (cms). The coefficient of variation of the scanner was 0.4%. Controls had their right hip measured, cases the non -fractured side. Measurements as mentioned earlier were within one week in fracture cases and at the time of the first visit in controls.

5.3.4 Analysis

Data was entered on EXCEL and descriptive analysis and intergroup comparisons using Mann Whiney U test carried out using SPSS version 7.5. Logistic regression was performed using STATA version 4.0.

5.4 RESULTS

5.4.1 Hip Axis Length In Community Controls

The mean age of the 100 community controls that had HAL measured was 75.1 years. The mean hip axis length was 12.1 cms, SD 0.8 cms and the range was 10.1-13.8 cms. HAL correlated with height (r_s=0.56; $p<0.05$) but not with age. There was no relation between HAL and BMD at any site.

5.4.2 Hip Axis Length In Men With Hip Fracture

Mean HAL in the 58 cases where measurements were made was 12.0 cms, SD 0.8 cms, and range 9.5-13.4 cms. Death, extreme frailty and co-morbid diseases explained the missing observations in 42 (42%). Amongst fracture cases, men who could have HAL measured (n=58) were younger (mean age (SD) 78.0 (10.1) Vs 82.6 (7.6); $p<0.01$) than those where measurements were not performed (n=42); there was no significant difference in height, weight

and body mass index. Comparing HAL between the two types of hip fracture there was no significant difference between cases with cervical (n=28) and trochanteric (n=30) hip fracture (mean (SD) 12.1(0.6) Vs mean (SD) 11.8 (0.8); p=NS). Also, comparing the anthropometric characteristics between these two groups there was no significant difference in age, height, weight or body mass index. There was no correlation of HAL with BMD at any site.

5.4.3 Comparison Between Cases And Controls

HAL was measured in 58 (58%) cases and 100 (100%) controls. Compared to controls, men with hip fracture were older and had significantly lower body mass index due to lower weight (Table 5.1). Differences in height were not significant. Hip axis length was similar in both groups (12 cms Vs 12.1 cms) and correlated with height (r=0.56, p<0.05) but not age.

Table 5.1 Characteristics of hip fracture cases and controls

Variable	**Hip Fracture** *n=58*	**Controls** *n=100*	
	Mean (SD)	**Mean (SD)**	**Significance**
Age (yrs)	78.0 (10.1)	75.1 (9.6)	NS
Height (cms)	171.2 (8.7)	170.6 (7.7)	NS
Weight (kg)	67.1 (10.6)	77.7 (16.3)	.01
Body mass index (kg/m^2)	23.2 (3.3)	26.7 (5.5)	.01
Hip axis length (cm)	12.0 (0.8)	12.1 (0.8)	NS

5.4.4 Hip Axis Length As Risk Factor For Hip Fracture

Using logistic regression there was no association between HAL and risk of hip fracture (Odds ratio [OR]=0.9 (95% CI 0.6, 1.3); this remained true after adjusting for height (OR=0.9 (95% CI 0.5, 1.5).

5.5 CONCLUSION

Results from this study indicate no association between HAL and risk of hip fracture in men. The mechanism by which HAL results in an increase in risk of hip fracture in women is unknown. Previous studies suggest that the risk persists after adjustment for body height and weight indicating it is not a surrogate for body size (itself linked with an increased risk of hip fracture). It

has been suggested that HAL is a marker for the ability of the femur or pelvis to absorb or avoid the impact of a fall. There are important gender differences in both the shape of the proximal femur and pelvis including the pelvic brim which may influence bone strength or resistance to fracture. It is possible that one or more of these shape parameters interact with HAL, and explain the discrepant findings in relation to fracture risk in men and women.

Osteoarthritis (OA) reduces HAL by reduction in hip joint space as a result of degenerative changes of the articular cartilage. OA is also associated with a reduced risk of hip fracture. These factors may confound the association between HAL and fracture risk. In our study there was no significant difference in the number of subjects with known OA between the two groups (chapter 3).

Height has recently been shown in several large prospective studies in men and women to be related to the risk of hip fracture. This may reflect longer hip axis length and increased mechanical impact. In our study there was a significant correlation between HAL and height consistent with earlier studies but there was no significant difference in height between our fracture cases and controls. Obesity is associated with a decreased risk of fracture. Weight and BMI were significantly different in our study but there was no correlation of HAL to BMI.

Results in this chapter suggest that assessment of hip axis length does not help predict hip fracture in men. Consequently, it should not be included in risk evaluation. It also highlights the need for caution in extrapolating the predictive risk of HAL observed in female Caucasians, to other populations. This study is limited by its cross sectional design; prospective data are required to confirm these findings.

6. ANDROGEN STATUS

6.1 SUMMARY

This chapter evaluates the male sex-hormone profile in a community population of elderly men, compares these with a matched hip fracture population, studies the effects of hip fracture on levels of androgens over 12 months and examines the relationships between androgen levels, bone density and risk of hip fracture.

In controls androgen levels declined modestly with age (r_s=-0.64, p<0.01). In parallel, there was an increase in the levels of gonadotrophins and binding globulins. Depending on the definition used 11 - 40% of the controls satisfied the criteria for diagnosis of hypogonadism (testosterone <9nmol/l or Free AI <30IU/l respectively). In the majority, primary testicular failure was the cause of the low androgens. Androgens also showed a significant positive correlation with BMD at all sites of the proximal femur (r_s=0.25, p<0.05) but not at the lumbar spine (r_s=0.19, p=NS). An inverse correlation was seen with bone markers (urinary cross links r_s=-0.27, p<0.01; osteocalcin r_s=-0.30, p<0.01).

Androgen levels were consistently lower in cases compared to controls from the time of fracture up-to 1-year. Hypogonadotrophic hypogonadism was the predominant cause. Chronic ill health reported earlier in the cases might be responsible for the hypogonadotrophic hypogonadism seen in fracture subjects. Hypogonadism (defined as Free AI <30IU/l) increased the risk for low trauma hip fracture 6 fold (odds ratio 6.34; 95%CI 2.32, 17.30)).

Androgens, gonadotrophins and sex hormone binding globulin showed a significant increase in levels between the time of fracture and 6 months with no further change at 1 year. Down-regulation of androgens around the time of the fracture secondary to the acute phase response may explain this finding.

The study has limitations. The two study groups were not perfectly age matched. Significant changes were noted in androgen levels between time of the fracture and 6 months. However, the combination of a case control design with longitudinal follow-up undoubtedly confirms low androgens as risk factors for hip fracture in men.

6.2 BACKGROUND

The importance of age, bone mineral density, and sex hormones on fracture risk in females is well established. Their role in men is not clear. Although, oestrogen deficiency is an established risk factor for fracture in women (Cummings *et al*, 1996), there is paucity of information on the role of androgens in hip fracture in men (Boonen *et al*, 1997). There is some evidence that gonadal hormones play a part in bone integrity of men (Rudman *et al*, 1994) analogous to their role in women. Young males with hypogonadism are known to develop osteoporosis (Finkelstein *et al*, 1996) which improves with testosterone replacement therapy (Francis *et al*, 1986). However, the impact of androgen deficiency on bones of older men is noted in only a few studies with very little data on its association with hip fractures (Boonen *et al*, 1997; Nyquist *et al*, 1998)).

Biochemical evidence of hypogonadism has been reported in up to 50% of men with hip fractures (Jackson *et al*, 1992, Stanley *et al*, 1991, Boonen *et al*, 1997). These 3 case control studies have limitations. They include small numbers (19-40 men only); cross sectional design, heterogeneity in timing of the samples (2 days to 18 months post fracture), incomplete hormonal work-up (no measurement of SHBG and gonadotrophins) and failing to control for physiological diurnal variation in hormone levels. The single longitudinal study by Nyquist and colleagues failed to find low testosterone as a risk factor for hip fracture. However, it looked at 10 hip fractures only and hence needs to be interpreted with caution.

A number of measures exist to assess androgen status in an individual. There is not much literature on levels of male sex hormones in the elderly. All laboratory reference ranges are derived from data in men aged 20-50 years. As a result it was considered appropriate to assess sex hormone status using a number of assays. Of the circulating testosterone in normal men, less than 4% is free (not protein bound). We therefore assessed both the free (free androgen index & free testosterone) and the bound forms (total testosterone) of the hormone along with its binding protein (SHBG) and the gonadotrophins (FSH and LH) to fully characterise each individual. To avoid sampling error induced by diurnal variation in hormone levels all samples were drawn early morning after an overnight fast. To study the effects, if any, of the acute stress of fracture on levels of these hormones in the perioperative period, longitudinal follow-up of both groups was planned for one year.

With this background, the role of androgens in low trauma hip fracture in men were examined by evaluating the following:

i) The androgen status of a randomly selected community population of elderly men

ii) The effects of hip fracture on male sex hormones from the perioperative period upto 1-year

iii) Difference in androgen levels between fracture cases and community controls

iv) Androgens as risk factors for hip fracture

6.3 METHODS

6.3.1 Study Design

100 consecutive men with low trauma hip fracture over a 14-month period were identified as cases. Simultaneously, an equal number of age matched controls were randomly recruited from the community. Details of study design and criteria used to recruit subjects in both arms of the study are given in Chapter 2.

6.3.2 Male Sex Hormone Status

Androgen status was assessed in both groups using 3 assays: serum testosterone, free androgen index (FAI) and free testosterone. In addition sex hormone binding globulin (SHBG) and the gonadotrophic hormones follicular stimulating (FSH) and luteinising hormone (LH) were also assayed. All measurements in both groups were performed at baseline, 6 and 12 months except for free testosterone, which was only measured at baseline, and 6 months due to the costs involved. Details of the assays used are outlined in Chapter 2.

Timing: Baseline blood samples were collected from the controls at the time of their first visit and in the fracture cases within 48 hours of admission. In both groups blood was drawn early morning after an overnight fast. This was to avoid error induced by potential physiological diurnal variation in hormone levels. Follow-up samples were collected at 6 and 12 months.

Algorithm used to characterise type of hypogonadism: In subjects with abnormal sex hormone results further endocrine evaluation followed an algorithm. Patients with

laboratory results consistently showing either normal testosterone (>9nmol/l) and / or free androgen index (>30IU/l) or a "primary" hypogonadal pattern (low testosterone (<9nmol/l) / free androgen index (<30 IU/l) with raised LH (>10 IU/l) and or FSH (>10 IU/l)) did not have further assessment. Those patients with consistently low testosterone and low gonadotrophins (FSH & LH <10 IU/l) suggestive of "secondary" hypogonadism were further investigated with measurement of cortisol and prolactin at baseline and at 6 months to confirm the cause. Free thyroxine was measured only if thyroxine was less than 70 at baseline. Magnetic resonance imaging (MRI) and or computerised tomography (CT Scan) of the pituitary was performed if prolactin values were over 2500 mIU/l on at least 2 occasions after excluding diseases or medications that may be responsible for these results. Dynamic pituitary function tests were not considered appropriate in the subjects because of their age.

6.3.3 Bone Markers

Urinary deoxypyridinoline was measured as a marker of bone resorption using second morning void urine samples observing an overnight fast. Serum osteocalcin was used to assess bone formation using fasting blood sample. Measurements were performed both at baseline and at 6 months Details of the assays used are outlined in Chapter 2 and further description of bone markers is given in Chapter 9.

6.3.4 Statistical Analysis

Descriptive statistics were used to describe individual subject characteristics. Univariate statistics, both parametric and non-parametric where appropriate were used to compare baseline characteristics between groups. Paired tests were used to determine change over time between groups. Logistic regression was used to explore the relationship between hip fracture and the putative risk factor. All analyses were adjusted for age.

6.4 RESULTS

6.4.1 Androgens In Community Dwelling Elderly Controls

Of the 100 community controls, 99, 94 and 85 men had samples drawn for androgen assay at baseline, 6 months and 1 year respectively. The single missing observation in the control

group at baseline was a result of the sample being misplaced in the laboratory. Mean androgen levels (using either assay) and LH were within the normal reference range of the laboratory at all three time points (Table 6.1). However mean SHBG and FSH were above the laboratories reference range at baseline, 6 months and 1 year. This may either be a result of the small sample size of our study or the exclusion of the very elderly men when routine reference ranges are derived for a laboratory generally based on populations aged between 20-50 years.

Table 6.1 Androgen status in controls over one year

	Normal ranges	**Initial**	**6 months**	**12 months**
		(n=99)	*(n=94)*	*(n=85)*
Testosterone (nmol/l)	***9-20***	14.1 (5.3)	14.0 (5.0)	14.9 (5.2)
Free androgen index (IU/l)	***30-200***	32.4 (12.4)*	28.6 (11.4)	28.1 (10.4)*
Free Testosterone (pg/ml)	***9-55***	9.2 (3.4)	10.4 (4.0)	NT
SHBG (nmol/l)	***10-40***	47.5 (17.3)*	52.4 (17.2)	55.7 (17.6)*
FSH (IU/l)	***1.1-9.4***	11.3 (14.6)	11.6 (14.6)	11.4 (14.0)
LH (IU/l)	***1.1-7.8***	5.5 (5.8)*	6.0 (5.7)	6.0 (4.3)*

Means and SDs are shown
* Wilcoxon signed ranks test $p<0.0001$

A modest correlation was observed between the three assays, namely testosterone, free androgen index and free testosterone amongst controls. Correlation (Spearman's) between testosterone and FAI was $r_s=0.43$ ($p<0.01$) and with free testosterone was $r_s=0.66$ ($p<0.01$). The two measures of bio-available testosterone (free AI and free TT) correlated better with each other $r_s = 0.83$ ($p<0.01$). Levels of FSH and LH were inversely related to androgen levels: FSH $r_s=-0.30$; LH $r_s=-0.55$ $p<0.01$, n=98

Prospective follow-up of this cohort over a one year period showed a significant decline in bio-available testosterone assessed using free androgen index: 32.4 IU/l initially, 28.7 IU/l at

6 months, and 28.1 IU/l at 1 year (Table 6.1). Using Wilcoxon signed ranks test of the 85 controls who had measurements both at baseline and at 1 year 61 (72%) showed a significant decrease in free androgen index; $p<0.0001$. This was accompanied by an increase in SHBG in 68 (80%) of the 85 controls; $p<0.0001$. An increase was also noticed in levels of both gonadotrophins (LH and FSH) although the increase in FSH did not reach statistical significance. Of the 85 controls who had measurement both at baseline and 1 year, an increase in LH was noted in 53 (62%) and in FSH in 40 (47%) men (Table 6.1).

The proportion of men with hypogonadism defined as free androgen index less than 30 IU/l increased with increasing age. The percentage (number) by decade was 0%(0), 6%(1), 7%(3), 21%(6) and 33%(1) from the fifth to ninth decade of life. The percentage fulfilling the criteria of hypogonadism also increased during the one-year follow-up. Androgen deficiency defined as serum testosterone <9.0 nmol/l was noted in 11/99 (11.1%) at baseline. Deficiency of bio-available testosterone, defined as free androgen index < 30.0 IU/l, was noted in 39/97 (40.2 %). At 6 months the numbers increased to 15/94 (16%) and 51/92 (55.4%) respectively. By 1 year they were 11/85 (12.9%) and 51/83 (61.4%).

Subjects with hypogonadism were further characterised into "primary" or "secondary" based on the algorithm described earlier (see section 6.3.2). At all time points the majority exhibited "primary" testicular failure as the cause of the hypogonadism. Initially 8 had low testosterone levels: 5 with primary gonadal failure (elevated LH/FSH) and with 3 secondary gonadal failure (depressed LH/FSH). At 6 months 13 had low androgen levels: 6 with elevated LH/FSH, 5 with depressed LH/FSH and 2 with isolated LH deficiency. Bilateral orchidectomies without testosterone replacement explained hypogonadism in 3 controls.

6.4.2 Correlation With Age, BMD And Bone Markers

Results from first visit were used to analyse correlation with other variables, as they were contemporary to BMD measurement. All 3 assays used to assess androgen status (serum testosterone, free androgen index and free testosterone) correlated well with each other $r_s=0.83$, $p<0.01$, $n=89$. With increasing age there was a modest decline in testosterone and bio-available testosterone; $r_s=-0.44$ and -0.64 $p<0.01$ respectively (Figure 6.1). By contrast, there was an increase with age in SHBG ($r_s=0.21$ $p<0.05$); LH ($r_s=0.42$ $p<0.01$) and FSH

(r_s=0.53 p<0.01), most marked in the eighth decade of life. Table 6.2 shows the age-related changes in androgen levels amongst community living elderly men.

A weak but positive relation was seen between androgens and BMD at all sites of the proximal femur: r_s =0.25, p<0.05, n=97. No correlation was seen with lumbar spine BMD (Table 6.3). A modest inverse relation was seen with bone markers (urinary deoxypyridinoline r_s=-0.28, p<0.01, n=93 and osteocalcin r_s=-0.30, p<0.05, n=70).

Table 6.2 Androgen status in community controls by decade

Variable	Age by decade				
	50-59	**60-69**	**70-79**	**80-89**	**90+**
	(n=8)	*(n=17)*	*(n=43)*	*(n=29)*	*(n=3)*
Testosterone (nmol/l)	14.7	16.5	14.8	11.9	8.2
Free Androgen Index (IU/l)	43.8	42.5	33.0	23.4	20.0
Free Testosterone (pg/ml)	11.2	12.6	9.4	6.8	5.2
SHBG (nmol/l)	37.4	41.6	47.4	54.3	44.0
FSH (IU/l)	16.9	5.1	7.5	17.2	28.1
LH (IU/l)	3.6	3.9	4.0	7.6	20.7

Means are shown

Figure 6.1 Free Androgen Index by Decade in Cases and Controls (Mean &95%CI are shown)

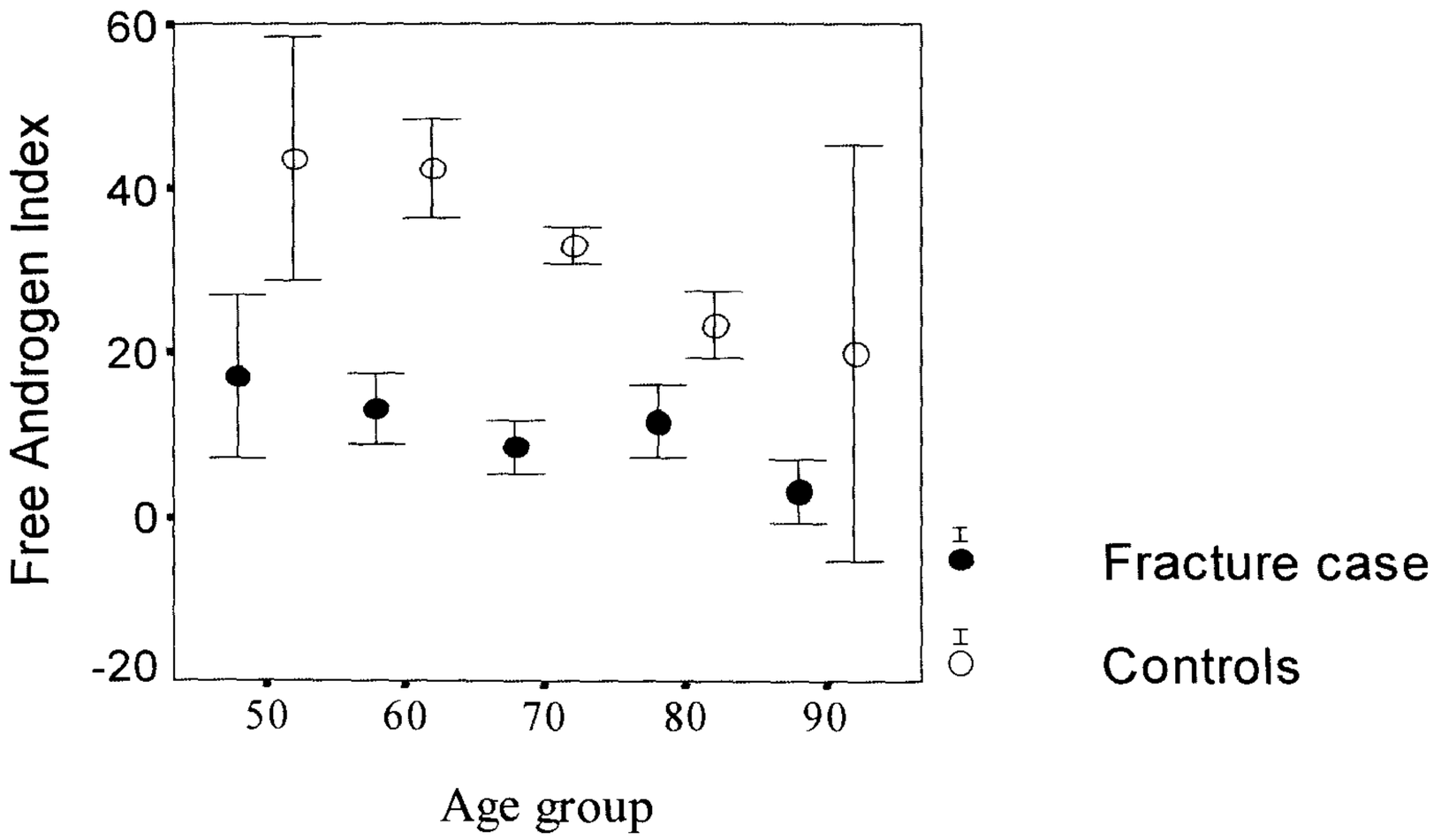


Table 6.3 Relationship with age, BMD and bone markers in controls

Variable	Testosterone		Free Androgen index	
	R_s	*Significance*	R_s	*Significance*
Age(yrs)	-0.44	<0.01	-0.64	<0.01
BMI(kg/m^2)	-0.21	<0.05	0.20	NS
BMD F Neck (g/cm^2)	0.28	0.01	0.25	0.01
BMD Intertrochanter (g/cm^2)	0.29	0.01	0.27	0.01
BMD Trochanter (g/cm^2)	0.32	0.01	0.27	0.01
BMD Ward's tr (g/cm^2)	0.26	0.01	0.31	0.01
BMD L Spine (g/cm^2)	-0.01	NS	0.19	NS
Urine Deoxypyridinoline	-0.35	0.01	-0.27	0.01
Osteocalcin (ng/ml)	-0.13	NS	-0.30	0.05

R_s = Spearman's Correlation Co-efficient

6.4.3 Androgen Levels At The Time Of The Fracture And Subsequent 12 Months

Androgen status was assessed within 48 hours of the fracture in 91 of the 100 hip fracture patients. Missing observations were due to death or difficulty in sampling. Mean testosterone, free testosterone and free androgen index were significantly below the normal range quoted in the laboratory (Table 6.4). Mean LH was within the range but mean SHBG and FSH were above the reference range. This discrepancy can be explained on the basis that normal laboratory ranges are derived from populations aged between 20-50 years.

At 6 months, of the 65 survivors, hormone measurements were possible in 51 cases (78.5%) following the strict early morning sampling technique after an overnight fast. The mean testosterone, free testosterone and free androgen index showed a significant increase from the perioperative period (almost doubling- refer Figure 6.2). They increased from an initial level of 4.1ng.ml, 3.8 pg/ml and 10.4 IU/l to 9.7ng/ml, 6.4pg/ml and 19.5IU/l respectively. Of the survivors (n=65), 51 cases had measurements carried out both at the time of the fracture and at 6 months. Compared to baseline 40 of the 51 (78%) showed an increase in testosterone, 39 (80%) an increase in free androgen index and 34 (76%) an increase in free testosterone (Wilcoxon signed ranks test $p<0.0001$). There was a concomitant but non-

significant increase in serum levels of SHBG, FSH and LH; they were 54.4nmol/l, 13.0IU/l and 7.5IU/l respectively compared to 44.8nmol/l, 9.8IU/l and 5.1IU/l at baseline.

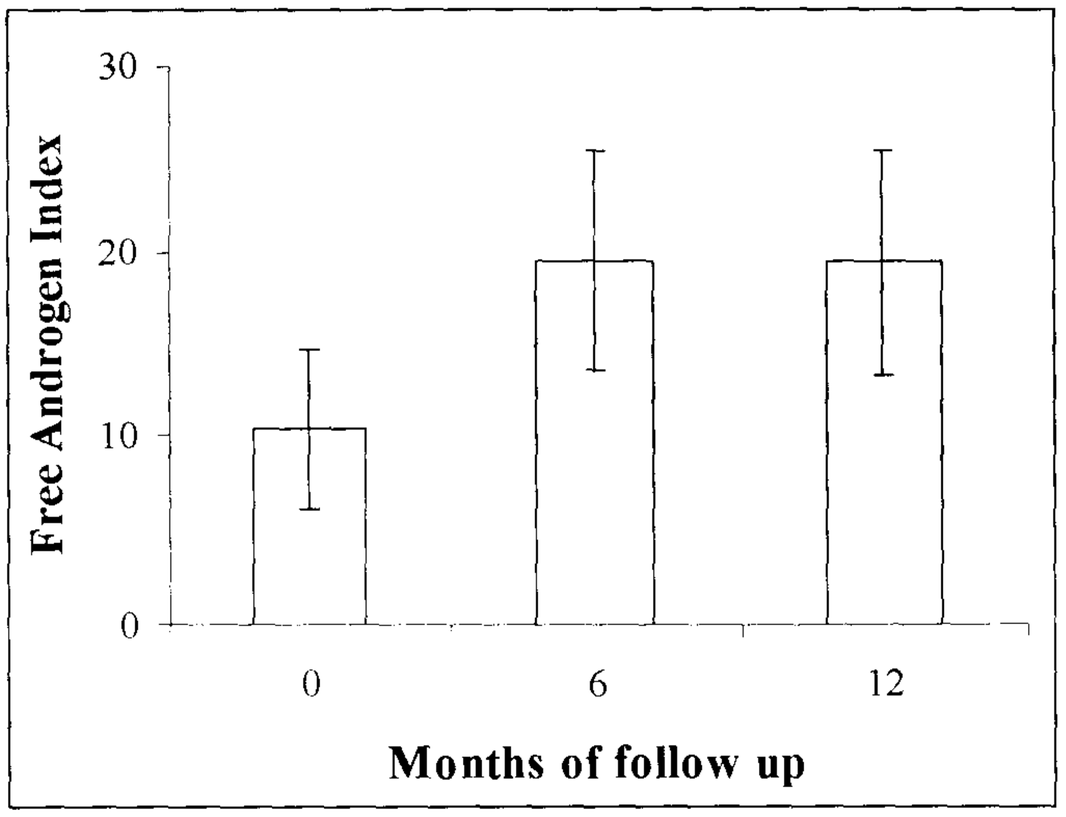
At one year of the 56 survivors repeat samples were possible in 41 cases (73.2%). No significant change was seen in mean testosterone and free androgen index between 6 months and 1 year; at 1 year they were 10.7ng/ml and 19.4IU/l respectively compared to 9.7ng/ml and 19.5IU/l at 6 months (see Figure 6.2). Free testosterone was not measured at 1 year due to expense of the assay. Using the Wilcoxon signed ranks test the mean ranks of the 36 cases that had measurements both at 6 months and 1 year were not significantly different. Similarly, there were no further changes seen in levels of SHBG, FSH and LH between 6 months and 1 year (Table 6.4).

Table 6.4 Androgen status in hip fracture cases

	Normal ranges	**Initial** *(n=91)*	**6 months** *(n=51)*	**12 months** *(n=41)*
Testosterone (nmol/l)	***9-20***	4.1(3.4)	9.7(5.2)	10.7(5.5)
Free androgen index (IU/l)	***30-200***	10.4(10.9)	19.5(11.2)	19.4(9.9)
Free Testosterone (pg/ml)	***9-55***	3.8(2.7)	6.4(3.6)	NT
SHBG (nmol/l)	***10-40***	44.8(19.2)	54.4(23.7)	59.0(24.6)
FSH (IU/l)	***1.1-9.4***	9.8(10.2)	13.0(11.9)	13.9(15.1)
LH (IU/l)	***1.1-7.8***	5.2(4.8)	7.5(12.3)	7.1(7.0)

Means and SDs are shown

Figure 6.2 Androgens in cases on admission, 6 and 12 months (mean/SE are shown)



6.4.4 Correlation With Age And Bone Markers

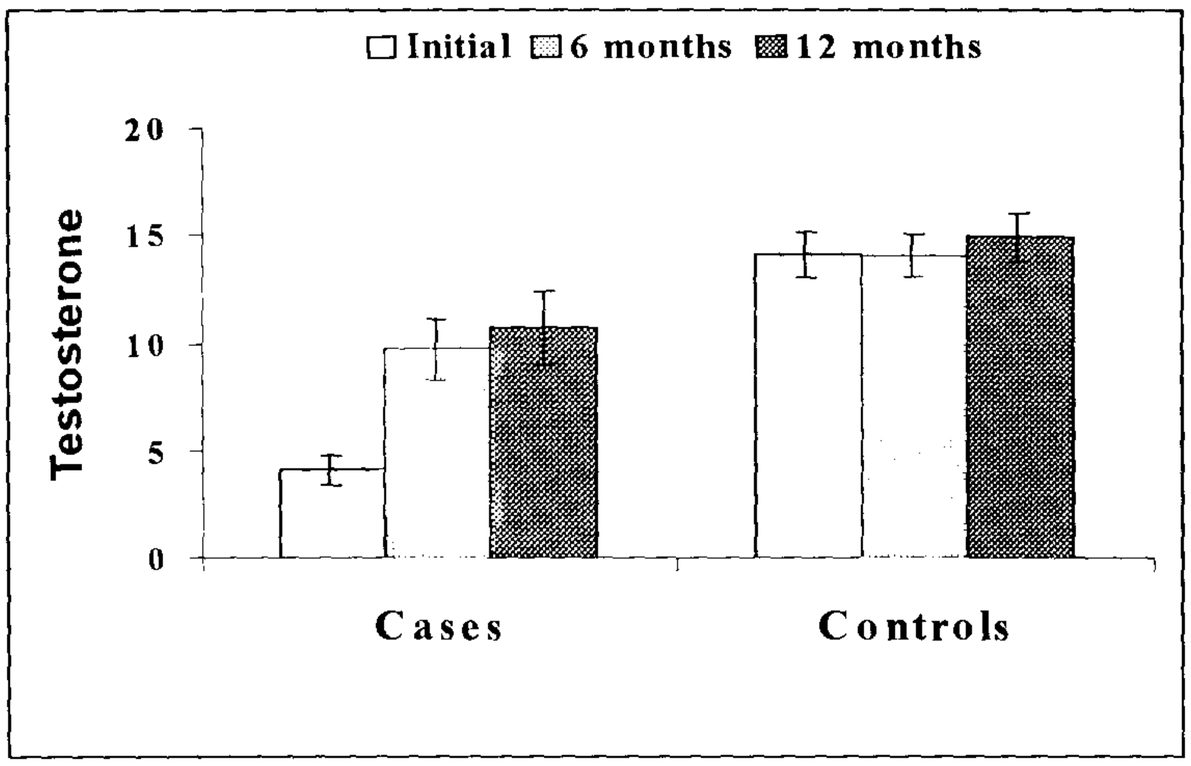
Androgen levels changed significantly from time of fracture upto 6 months and subsequently stabilised. Therefore, levels at 6 month represent the best conservative pre-fracture estimate for an individual. However, due to the high mortality and hence reduced number of cases with repeat measurements at 6 months a selection bias may confound the association between androgen levels and the variables under study. Unlike controls it was therefore considered inappropriate to examine correlation between androgens and other variables in the fracture group.

6.4.5 Androgen Status In Hip Fracture Cases Compared To Community Controls

Androgen levels were available in 91 cases within 48 hours of the fracture and in 99 controls at the time of their first visit. At 6 months 51 of the 65 fracture survivors and 94 of the 99 controls underwent repeat hormone measurements. At 1 year, the figures were 41 of 56 and 85 of 94 respectively.

Significantly lower levels of testosterone, free androgen index and free testosterone were observed in cases at the time of the hip fracture, at 6 and 12 months compared to controls ($p<0.001$). These differences persist even after adjusting for age and body mass index (Figure 6.3 & Table 6.5). No differences were seen in levels of SHBG, FSH and LH between the two groups at any time point.

Figure 6.3: Change in total serum testosterone in cases and controls over 1 year



This was also true when repeat analysis was performed comparing the two groups by decade. Comparing the number (%) of subjects with hypogonadism a significantly higher proportion fulfilled the criteria amongst cases as opposed to controls. Androgen deficiency defined as serum testosterone <9.0ng/ml was noted in 81/91 (89%) of fracture cases versus only 11/99 (11.1%) of the controls (OR 64.8, 95%CI 26.1, 160.7) at outset. Deficiency of bio-available testosterone, defined as free androgen index < 30.0IU/l, was noted in 85/90 (86.7 %) of fracture cases versus only 39/97 (40.2 %) of the controls (OR 25.3, 95%CI 9.4, 68.0). At 6 months, low testosterone was present in 25/51 (49%) cases compared to 15/94 (16%) controls (OR 5.1, 95%CI 2.3, 11.0). Similarly, low bio-available testosterone was present in 44/50 (88%) cases compared to 51/92 (55.4%) controls (OR 5.9, 95%CI 2.3, 15.2).

Detailed work-up of individuals based on their androgen status and the gonadotrophin response revealed a mixed picture of "primary" and "secondary" hypogonadism in both groups, significantly more in hip fracture cases than controls. Initially 78 fracture cases had low androgen levels (testosterone<9nmol/l and free AI<30IU/l): 14 with primary gonadal failure (LH/FSH elevated), 48 secondary gonadal failure (LH/FSH depressed), 12 mixed abnormalities and 4 indeterminate. Of the survivors, at 6 months 22 cases had low androgen levels: 7 with elevated LH/FSH and 8 depressed LH/FSH levels. Bilateral orchidectomies explained primary hypogonadism in 3 fracture cases. Two cases had hyperprolactinaemia (levels > 1500mIU/l) suggesting secondary hypogonadism both at the time of the fracture and at 6 months. CT Scan head of the only survivor did not show any pituitary abnormality. Dynamic pituitary function tests were not considered ethical in view of the patients' age and poor general health status.

In the controls 8 had initial low testosterone levels: 5 with elevated LH/FSH, 3 depressed LH/FSH and none had mixed pattern. At 6 months 13 controls had low androgen levels: 6 with elevated LH/FSH and 5 depressed LH/FSH and 2 isolated LH deficiency. Bilateral orchidectomies explained hypogonadism in 3 controls

Prospective follow-up of both groups over 1 year showed a significant increase in androgen and gonadotrophin levels in cases from time of fracture upto 6 months with no further

change at 1 year. In contrast there was a significant reduction in bio-available testosterone with accompanying rise in SHBG, FSH and LH in the controls. This increase reached significance for SHBG and LH (Wilcoxon signed ranks test $p<0.001$).

Table 6.5 Sex hormone levels at baseline, 6 and 12 months in controls and cases

Variable	Normal Range	Controls		
		Initial	6 months	12 months
		(n=99)	*(n=94)*	*(n=85)*
Testosterone	***9-20***	14.1(5.3)	14.0(5.0)	14.9(5.2)
Free AI	***30-200***	32.4(12.4)	28.6(11.4)	28.1(10.4)
Free testos	***9-55***	9.2(3.4)	10.4(4.0)	NT
SHBG	***10-40***	47.5(17.3)	52.4(17.2)	55.7(17.6)
FSH	***1.1-9.4***	11.3(14.6)	11.6(14.6)	11.4(14.0)
LH	***1.1-7.8***	5.5(5.8)	6.0(5.7)	6.0(4.3)

Variable	Normal Range	Fracture Cases		
		Initial	6 months	12 months
		(n=91)	*(n=51)*	*(n=41)*
Testosterone	***9-20***	4.1(3.4)	9.7(5.2)	10.7(5.5)
Free AI	***30-200***	10.4(10.9)	19.5(11.2)	19.4(9.9)
Free testos	***9-55***	3.8(2.7)	6.4(3.6)	NT
SHBG	***10-40***	44.8(19.2)	54.4(23.7)	59.0(24.6)
FSH	***1.1-9.4***	9.8(10.2)	13.0(11.9)	13.9(15.1)
LH	***1.1-7.8***	5.2(4.8)	7.5(12.3)	7.1(7.0)

Mean values (SD) are shown

Statistical notes

Differences on Mann-Whitney U test

Controls vs. Cases at 0, 6 and 12 months $p<0.0001$

Differences on Wilcoxon Signed Rank test

Cases at 0 vs. at 6 and 12 months $p<0.0001$

Cases at 6 vs. at 12 months NS

Controls at 0 vs. 6 and 12 months NS

6.4.6 Testosterone As A Risk Factor For Hip Fracture

Logistic regression was used to assess androgens as risk factors for hip fracture. The 6-month data were used since, from the earlier analysis it is clear that androgen levels are altered when measurements are performed at the time of the fracture and that they stabilise by 6 months.

Table 6.6 shows the reduction in risk of fracture per unit increase in male sex hormone level. After adjusting for age and body mass index the risk of hip fracture decreased by 16% per 1 unit increase in androgen levels: testosterone- OR=0.84, 95%CI 0.77, 0.92 and free androgen index- OR=0.93, 95%CI 0.89, 0.98. No difference was noted in the amount of risk conferred by low androgen levels when repeat analysis was performed using age alone or both age and body mass index in the regression equation.

Table 6.6: Estimates of risk from logistic regression

	Per unit change in androgens		
	Unadjusted	**Adjusted for age**	**Adjusted for age and BMI**
Testosterone (/nmol/l)	0.85 (0.79, 0.92)	0.85 (0.78, 0.92)	0.84 (0.77, 0.92)
Free AI (/IU/l)	0.92 (0.89, 0.96)	0.91 (0.87, 0.95)	0.93 (0.89, 0.98)
	By presence/absence of hypogonadism		
	Unadjusted	**Adjusted for age**	**Adjusted for age and BMI**
Testosterone < 9.0nmol/l	5.06 (2.32, 11.03)	4.91 (2.21, 10.94)	4.44 (1.72, 11.44)
Free AI < 30.0 IU/l	5.90 (2.29, 15.20)	6.34 (2.32, 17.30)	3.61 (1.23, 10.60)

Odds ratio with 95% confidence interval are shown
The analyses are based on measurements at 6 months. Results show raw data; after adjusting for age and for both age and body mass index.

"Hypogonadism" was defined as serum levels less than the lower limit of the normal reference range for the assay in question at 6 months (i.e. testosterone <9ng/ml and Free AI < 30IU/l). Using logistic regression after adjusting for age and body mass index, presence of hypogonadism increased the risk of hip fracture over 4 fold. OR range: 3.6 (95 %CI 1.2,

10.6) to 4.4 (95%CI 1.7, 11.4) Table 6.6. When free AI was evaluated as a risk factor for fracture a reduction in risk was observed when adjustment for BMI was made (OR 6.9-3.6). This may be explained on the basis that free AI is dependent on SHBG levels, which in turn correlates with BMI.

6.5 CONCLUSIONS

A number of conclusions can be drawn from the analysis carried out in this chapter. All three assays used to assess androgen status correlate well with each other although assays for the unbound (free) form of the hormone correlate better with each other; r_s=0.83; p<0.01.

In men living in community there is a gradual decline of male sex hormones with advancing age. Free hormone (free testosterone and free AI) is more sensitive to change (r_s =-0.64; p<0.01) due to increase with age in the sex hormone binding globulin. It may therefore be argued that in this age group, measurement of free hormone might be superior in assessing individuals' sex hormone status. 40% of elderly men in the community exhibit biochemical evidence of hypogonadism. In the majority "primary" gonadal failure is the cause of this hypogonadism.

A significantly higher proportion of men with low trauma hip fracture have biochemical evidence of hypogonadism; this varies from 80% if measurements are performed at the time of fracture to 53% (22/51) amongst survivors at 6 months. In the majority (46/78) the biochemical profile points towards "secondary" or hypogonadotrophic hypogonadism as the cause of the low hormone. The latter is known to be associated with chronic ill health.

Tracing the androgen levels upto a year following the hip fracture raises the possibility of an acute inhibitory effect of fracture per se on hormone levels which normalises by 6 months. Hence, in the setting of an acute illness, timing of the samples is very crucial for accurate hormone assessment.

Cases showed consistently lower levels of androgens compared to controls at baseline, 6 months, 1 year, as a group, by decade and even after controlling for age and BMI. Results

from multiple logistic regression confirm low androgen levels to be a risk factor for hip fracture in men; the risk decreasing by 15-18% per unit increase in androgen levels. As a corollary, presence of biochemical hypogonadism increases the risk of hip fracture by 4-6 fold in men aged 50 years and over.

Androgens also show a small but significant positive correlation with BMD (r_s =0.25, $p<0.05$) and an inverse relation with both urinary deoxypyridinoline and osteocalcin. It may therefore be conjectured that by regulating the rate of bone turnover androgens affect bone strength & quality and influence fracture risk.

Some of the inherent constraints imposed by using a case-control design have been overcome by prospective follow-up of both groups for one year. Results clearly show a strong association between low male sex hormones and low trauma hip fracture in men. The factors underlying the development of hypogonadism and the mechanism by which it influences fracture risk can only be debated as the study was not designed to answer these questions.

7. OESTRADIOL

7.1 SUMMARY

This chapter initially examines total serum oestradiol levels in a randomly selected community population of elderly men and compares the findings with a matched hip fracture population. It then studies the effect of hip fracture on levels of oestradiol over a 6-month period and examines the relationship between oestradiol, bone density and risk of hip fracture.

Total oestradiol levels in the community controls were within the reference range for healthy younger men (aged 20-50 yrs) and correlated with CRP (r_s=0.24; p<0.01, n=98), serum albumin (r_s=-0.23; p<0.01, n=97) and BMD (femoral neck r_s=0.25; p<0.01, n=98). No correlations were seen with age, BMI or testosterone. These associations were stronger with free oestradiol calculated from a ratio of serum total oestrogen and sex hormone binding globulin. In order of importance, free androgen index, testosterone, age and serum albumin influenced free oestradiol levels in the controls. Together they explained 40% of the variance in free oestradiol levels. Free oestradiol was the most important sex steroid in predicting BMD. As an example, together with free androgen index, family history of osteoporosis and past history of fracture, it explained 27% of the variance in BMD at the femoral neck.

Cases had significantly higher total oestradiol and free oestradiol levels compared to controls (p<0.001) at the time of the fracture, although they were still within the reference range. Level of both forms of the hormone reduced significantly 6 months post fracture (p<0.01 by Wilcoxon signed rank test), such that free oestradiol reached values comparable to those in the controls. Concomitantly, significant alterations in the acute phase reactants namely C-reactive protein and serum albumin was noted.

The role of oestradiol as a risk factor for hip fracture is not certain from this study. After adjusting for C-reactive protein and using the data at 6 months both total oestradiol (Odds ratio 0.98, 95%CI 0.97, 0.99) and free oestradiol (Odds ratio 0.34, 95%CI 0.02, 6.1) conferred protection although the values did not attain significance when free oestradiol was used in the analysis.

7.2 BACKGROUND

Recent studies on osteoporosis in men have suggested that oestrogens may play a key role as in women (Khosla *et al*, 1998). Mutations in the oestrogen receptor gene and genes coding for the enzyme aromatase, which is responsible for the conversion of androgens to oestrogen's, have been reported in case reports of men with severe osteoporosis (Morishima *et al*, 1995). Treatment with oestrogen but not testosterone markedly increased BMD in these individuals (Carani *et al*, 1997). In a recent open trial of testosterone administered to eugonadal men with vertebral crush fractures, increase in BMD was significantly correlated with change in oestradiol but not testosterone levels (Anderson *et al*, 1997). The recent prospective study found that serum oestradiol but not testosterone was positively associated with BMD in men over age 65 years (Slemenda *et al*, 1997). Furthermore a recent epidemiological study (Khosla *et al*, 1998) showed correlation of BMD with bioavailable not total testosterone and with both total and bioavailable oestradiol. The authors also demonstrated that bioavailable oestradiol was the more important sex steroid in predicting femoral neck BMD supporting the hypothesis that oestrogen's play a key role in influencing BMD in men as in women.

However, except for the study by Khosla *et al* previous studies are limited in studying subjects in a narrow age range and have failed to measure levels of free sex steroids. The latter is the fraction that is available to tissues and unaffected with increasing SHBG with age. Most studies have addressed the issue with testosterone or oestradiol but not with both. There have been no studies looking at men with osteoporotic fractures, nor have there been any case control studies.

With this background this chapter examines the role of oestradiol in low trauma hip fracture in men by evaluating the following:

i) Oestradiol levels in a randomly selected community population of elderly men

ii) Comparison of oestradiol levels between community controls and hip fracture cases

iii) The effects of hip fracture on levels of oestradiol from the time of the event to one year

iv) Oestradiol levels as risk factors for low trauma hip fracture

7.3 MATERIAL & METHODS

7.3.1 Study Design

100 consecutive men with low trauma hip fracture were recruited as cases over a 14-month period. Simultaneously, an equal number of men were randomly recruited from the community as controls. Details of the study design and criteria used are given in Chapter 2.

7.3.2 Oestradiol Assay

Female sex-hormone status was evaluated in both groups by measuring serum oestradiol at baseline and at 6 months. Details of the competitive immunoassay used to measure oestradiol levels are given in Chapter 2. Free oestradiol was calculated as the ratio between oestradiol (in nmol/l) and sex hormone binding globulin.

Initial samples were collected in the control population at the time of their first visit and in fracture cases within 48 hours of admission. Subsequent samples were collected in both groups at 6 months. Blood samples for the assay were collected early morning after an overnight fast to avoid error induced by physiological diurnal variation. This also ensured homogeneity in the sampling technique.

7.3.3 Statistical Analysis

Descriptive statistics were used to describe group characteristics in both cases and controls. Univariate statistics, both parametric and non-parametric where appropriate were used to compare baseline values between groups. Paired tests were used to determine change over time between groups. Logistic regression was used to explore the relationship between hip fracture and the putative risk factor i.e. oestradiol levels. Multiple linear regression using backward elimination with the probability of "F" to eliminate set at >0.1 and "T" to include set at $p<0.05$ was used to create models of BMD and oestradiol prediction. All analysis was adjusted for age.

7.4 RESULTS

7.4.1 Oestradiol In Community Dwelling Men

Total oestradiol levels in the controls (mean 106 pmol/l; SD 50) were within the reference range (<180 pmol/l) stated in the manufacturers kit for healthy younger men both at baseline and at 6 months (Table 7.1).

Table 7.1 Oestradiol levels in controls at baseline and at 6M

Variable	N range	*Time*	No.	Mean	SD	Signif*
Age (years)		***Baseline***	100	75.0	9.6	
BMI (kg/m^2)	20-25	***Baseline***	97	26.7	5.5	
C-Reactive Protein (mg/l)	0-10	***Baseline***	100	3.0	5.4	
Oestradiol (pmol/l)	<180	***Baseline***	98	106.2	50.4	
		6M	90	121.5	37.9	<0.001
SHBG (nmol/l)	10-40	***Baseline***	97	47.5	17.3	
		6M	92	52.4	17.2	NS
Free oestradiol		***Baseline***	95	0.26	0.18	
		6M	89	0.26	0.13	NS

Means and SDs are shown
* Wilcoxon signed ranks test between baseline and 6 months

A significant increase in total oestradiol levels was noted at 6 months ($p<0.001$) compared to baseline (Table 7.1) using the Wilcoxon signed ranks tests. Fifty-six of the 88 subjects tested at both time points showed an increase. In contrast, free oestradiol levels (calculated as the ratio between oestradiol in nmol/l and SHBG) did not change. Of the 84 controls who had measurements at both time points, 44 showed an increase and 40 a decrease in free oestradiol levels (Wilcoxon signed ranks test p=NS). High total oestradiol levels defined as

more than 180 pmol/l were present in 8/98 (8.2%) controls at baseline and in 4/90 (4.4%) at 6 months.

The factors influencing free oestradiol levels were explored by multiple linear regression using backward elimination (Table 7.2). Serum levels of free androgen index (FAI); testosterone, albumin and age in combination explained 40% of the variance in free oestradiol levels. Male sex steroid levels (FAI and testosterone) were the principal determinants.

Table 7.2 Factors influencing free oestradiol levels in controls
Backwards linear multiple regression model

Variable	B	95% CI	Significance
Age	0.005	0.001, 0.009	0.02
Free androgen index	0.012	0.009, 0.015	0.0001
Testosterone	-0.012	-0.018, -0.006	0.0002
Serum albumin	-0.004	-0.020, 0.001	0.07
Constant	0.09	-0.42, 0.61	0.72

Variables not in the equation: height, weight, C-reactive protein and serum globulin

Multiple R = 0.65; Adjusted R Square = 0.40

Total oestradiol levels correlated with C-reactive protein and serum albumin (r_s =0.24; p=0.017, n=98 and r_s =-0.23; p<0.025, n=97 respectively) but not with age (r_s= 0.02), body mass index (r_s=0.06), testosterone (r_s =0.09) and bone markers (r_s =0.02) as shown in Table 7.3. By contrast, free oestradiol levels correlated with all [body mass index (r_s=0.29, p=0.005); free androgen index (r_s=0.48; p<0.001); free testosterone (r_s =0.42; p<0.001); C-reactive proteins (r_s =0.33; p<0.001); albumin (r_s =-0.24; p=0.02)] except age (r_s=-0.15) and bone markers (r_s =0.02) Table 7.3.

Table 7.3 Relationship with age, BMI, C-reactive protein and S Albumin in controls

Variable	Oestradiol		Free Oestradiol	
	r_s	*Significance*	r_s	*Significance*
Age(yrs)	0.02	NS	-0.15	NS
BMI(kg/m^2)	0.06	NS	0.29	0.005
C-reactive protein (mg/l)	0.24	0.02	0.33	0.001
S Albumin (g/l)	-0.23	0.03	-0.24	0.02
Free androgen index (IU/l)	0.16	NS	0.48	0.01
Free testosterone (pg/ml)	0.32	.01	0.42	0.01
Urine Dpd	0.02	NS	0.02	NS
Osteocalcin (ng/ml)	-0.09	NS	-0.16	NS

r_s = Spearman's Correlation Co-efficient

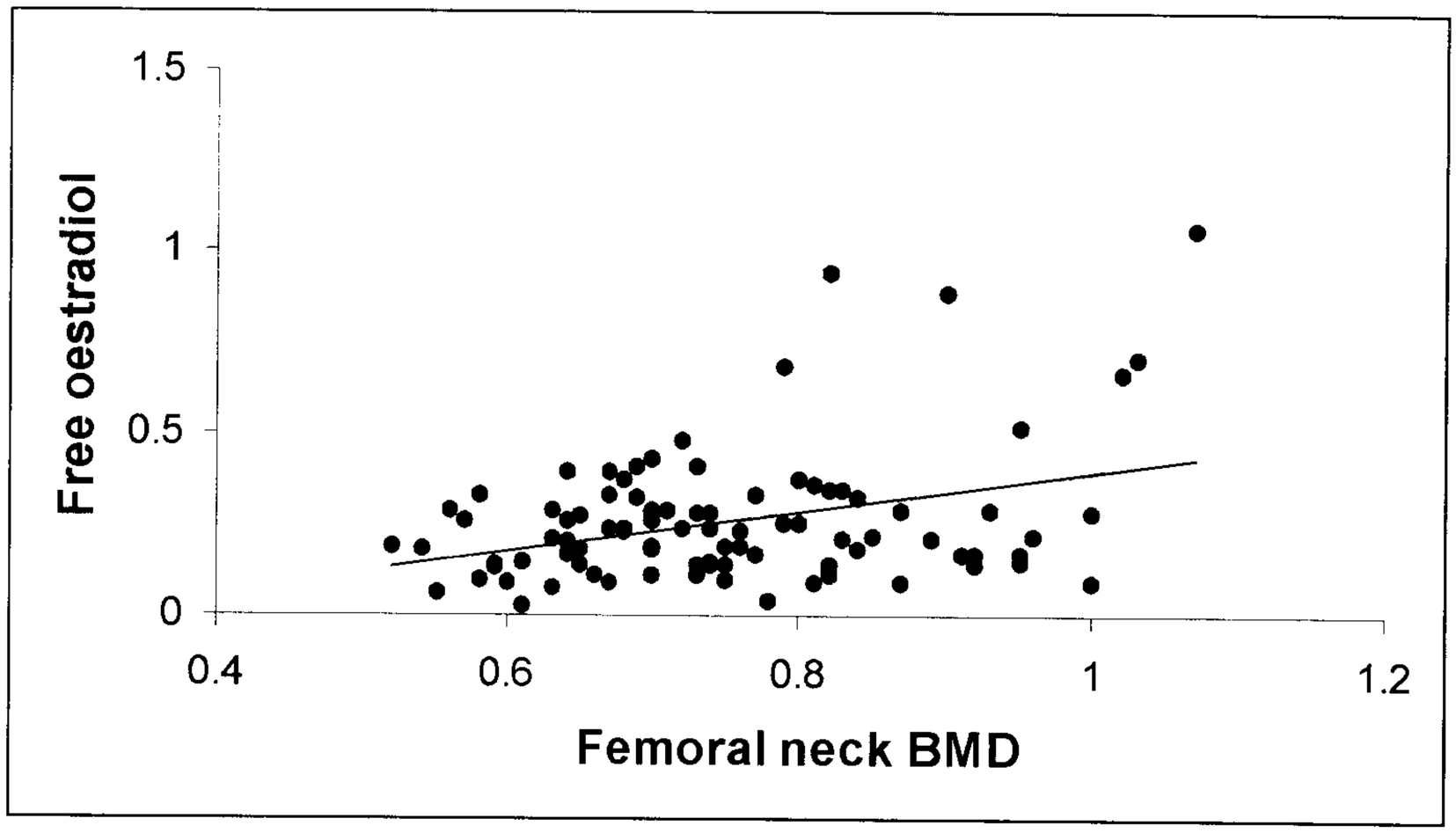
Table 7.4 Partial correlation coefficients (corrected for age) between BMD and oestradiol

Site	Oestradiol		Free Oestradiol	
	r_s	*Significance*	r_s	*Significance*
Lumbar spine	0.28	0.007	0.33	0.001
Femoral neck	0.40	0.001	0.43	0.001
Inter-trochanteric	0.25	0.004	0.27	0.006
Trochanteric	0.29	0.001	0.32	0.002
Ward's triangle	0.37	0.001	0.43	0.001

r_s = Spearman's correlation coefficients

After adjusting for age, both total and free oestradiol levels exhibited good correlation with BMD (Table 7.4). The correlation between free oestradiol and femoral neck BMD (r_s =0.43) is shown in Fig 7.1. The correlations were better with all sites of the proximal femur than with the lumbar spine. The relationship was stronger with free oestradiol than with total oestradiol.

Figure7.1 Free oestradiol and femoral neck BMD in controls



The interactions between free oestradiol and other factors influencing BMD were explored using multiple linear regression using backward elimination (Table 7.5 & 7.6). Free oestradiol levels were the most important sex steroid predicting BMD at all sites. Together with weight, free androgen index, family history of osteoporosis and past history of fracture they explained 27% of the variance in femoral neck BMD (Table 7.5). Similarly, with age, weight and past history of fractures they explained 25% of the variance in BMD at the lumbar spine (Table 7.6).

Table 7.5 Factors influencing femoral neck BMD in controls.
Backwards linear multiple regression model

Variable	B	95% CI	Significance
Weight	0.002	0.000, 0.004	0.02
Free androgen index	0.002	0.000, 0.005	0.04
Free oestradiol	0.222	0.06, 0.39	0.009
Sex hormone binding globulin	0.002	0.001, 0.004	0.01
Past history of fracture	0.05	-0.004, 0.09	0.07
Family history of osteoporosis	0.09	0.02, 0.16	0.01
Constant	0.07	-0.19, 0.334	0.59

Variables not in the equation: age, height, C-reactive protein, haemoglobin, calcium, serum albumin, serum globulin, vitamin D, family history of fracture

Multiple R= 0.56; Adjusted R Square = 0.27

Table 7.6 Factors influencing lumbar spine BMD in controls. Backwards linear multiple regression model

Variable	B	95% CI	Significance
Age	0.002	0.002, 0.01	0.004
Weight	0.002	0.002, 0.008	0.002
Free oestradiol	0.113	0.06, 0.51	0.01
Past history of fracture	0.04	-0.01, 0.16	0.07
Constant	0.23	-0.45, 0.479	0.97

Variables not in the equation: height, C-reactive protein, haemoglobin, calcium, serum albumin, serum globulin, sex-hormone binding globulin, vitamin D, free androgen index, family history of fracture and osteoporosis

Multiple R= 0.53; Adjusted R Square = 0.25

7.4.2 Oestradiol Levels In Men With A Hip Fracture

Total oestradiol levels were within the manufacturers normal reference range for healthy younger men both at the time of the hip fracture and at 6 months. In the immediate post-fracture period total oestradiol levels were significantly raised compared to those at 6 months ($p<0.001$). This observation remained true even after adjusting for SHBG and analysing levels of free oestradiol (Wilcoxon signed ranks test $p<0.001$- Table 7.7). Of the 45 survivors who had measurements both at the time of the hip fracture and at 6 months, 30 showed a decrease in total oestradiol levels from the time of the incident event ($p<0.01$ by Wilcoxon signed rank test) Table 7.7. Similar changes were seen in free oestradiol. Elevated total oestradiol, defined as levels above 180 pmol/l, were seen in 27/90 (30%) cases around the time of the fracture and in only 3/49 (6.1%) at 6 months.

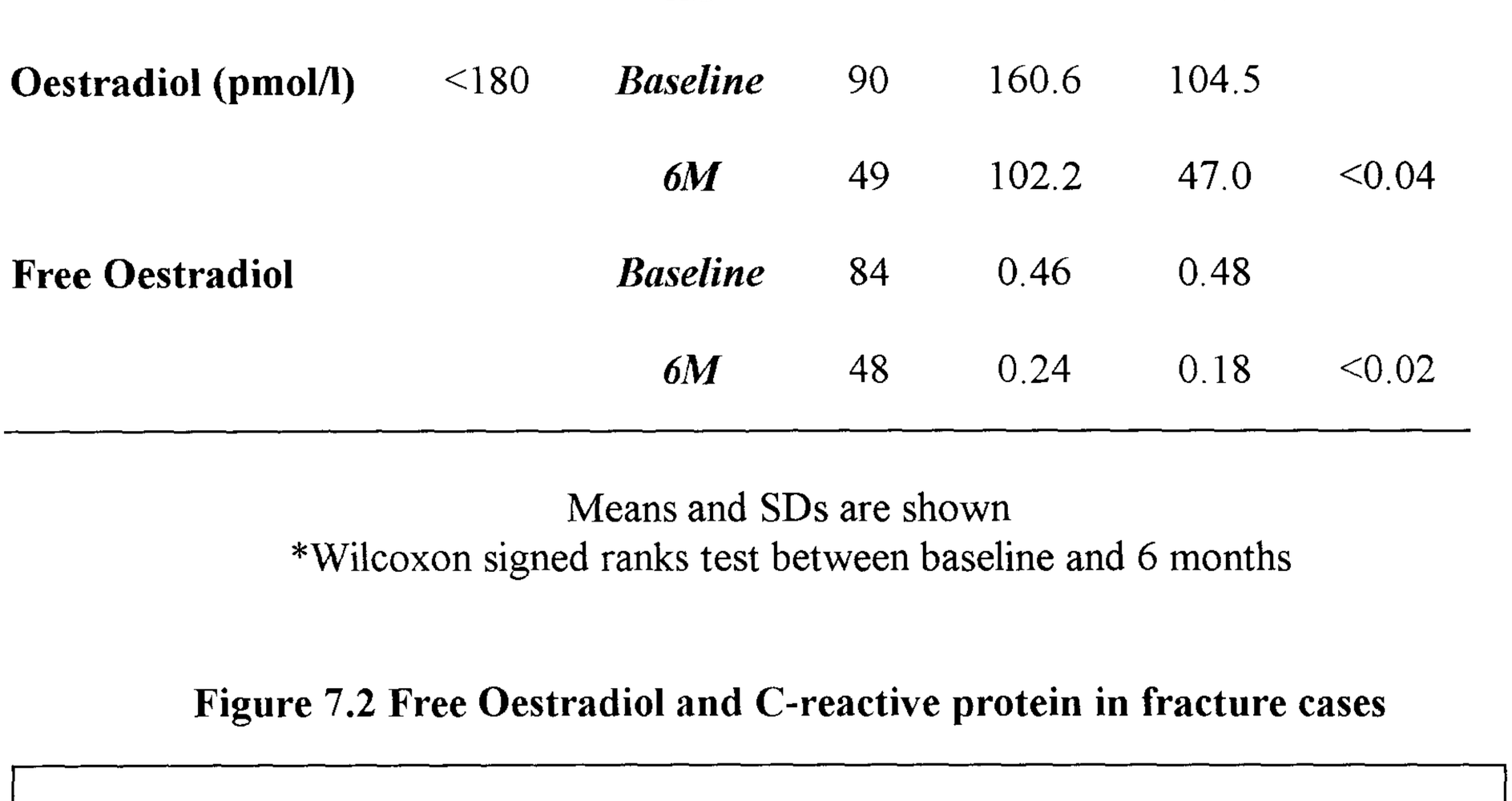
There was a modest correlation between total oestradiol, C-reactive protein and serum albumin (r_s =0.25; p=0.027, n=77 and r_s =-0.28; p=0.007, n=89 respectively). Similar correlation's were seen with free oestradiol (r_s =0.23; p=0.048, n=74 and r_s =-0.27; p=0.013, n=83 respectively). The correlation between free oestradiol and C-reactive protein is shown in Figure 7.2.

Table 7.7 Oestradiol levels in cases following hip fracture and at 6M

Variable	N range	*Time*	No.	Mean	SD	Signif*
Age (years)		***Baseline***	100	79.9	9.4	
BMI (kg/m^2)	20-25	***Baseline***	72	23.4	3.3	
SHBG (nmol/l)	10-40	***Baseline***	90	44.8	19.2	
		6M	50	54.4	23.7	<0.001
Oestradiol (pmol/l)	<180	***Baseline***	90	160.6	104.5	
		6M	49	102.2	47.0	<0.04
Free Oestradiol		***Baseline***	84	0.46	0.48	
		6M	48	0.24	0.18	<0.02

Means and SDs are shown
*Wilcoxon signed ranks test between baseline and 6 months

Figure 7.2 Free Oestradiol and C-reactive protein in fracture cases



r_s = 0.23; p=0.05

7.4.3 Comparison of Oestradiol Levels Between Hip Fracture Cases And Controls

The hip fracture cases were significantly older and had lower mean BMI compared to the controls (Table 7.8). There was no significant difference in mean SHBG values between cases and controls despite a significant increase in serum levels within the fracture group between time of fracture and 6 months (Wilcoxon signed rank test $p<0.05$).

Table 7.8 Differences between cases and controls

Variable	N range	*Time*	Cases		Controls		*Sig*
			No.	*Mean (SD)*	*No.*	*Mean (SD)*	*Mann Whitn*
Age (years)		***Baseline***	100	79.9 (9.4)	100	75.1 (9.6)	<0.01
BMI (kg/m^2)	20-25	***Baseline***	72	23.4 (3.3)	97	26.7 (5.5)	<0.0001
C-reactive protein(mg/l)	0-10	***Baseline***	82	120.5 (76.4)	100	3.0 (5.4)	<0.0001
		6months	49	10.9 (19.4)	92	1.5 (4.5)	<0.0001
SHBG (nmol/l)	10-40	***Baseline***	90	44.8 (19.2)	97	47.5 (17.2)	NS
		6months	50	54.4 (23.7)	92	52.4 (17.2)	NS
Oestradiol (pmol/l)	<180	***Baseline***	90	160.6 (104.5)	98	106.2 (50.4)	<0.0001
		6months	49	102.2 (47)	90	121.5 (37.9)	<0.005
Free Oestradiol		***Baseline***	84	0.46 (0.48)	95	0.26 (0.18)	<0.0001
		6months	48	0.24 (0.18)	89	0.26 (0.13)	NS

Means and SDs are shown

Levels of both total and free oestradiol were significantly higher in cases compared to controls at the time of the fracture when analysed per se and after adjusting for age and BMI (data not shown). Differences in total but not free oestradiol persisted upto 6 months (Table 7.8). A significant reduction was observed in both total and free oestradiol levels within the fracture group from the time of the fracture to 6 months (Wilcoxon signed rank test $p<0.05$). Concomitantly, levels of C-reactive proteins were significantly higher in cases compared to controls both at the time of the fracture and at 6 months despite a significant

reduction in CRP levels within the fracture cohort between the two time points (Wilcoxon signed rank test $p<0.01$).

7.4.4 Oestradiol Levels As A Risk Factor For Hip Fracture

Due to significant changes noted in serum levels of both total and free oestradiol from the time of fracture to 6 months and their correlation with the acute phase reactants (C-reactive proteins and serum albumin) the 6 month data was considered appropriate for evaluating oestradiol as a risk factor for hip fracture.

Using multiple logistic regression, one picomol increase in total oestradiol levels reduces the risk of low trauma hip fracture by 1%. This is unchanged after controlling for age, body mass index and C-reactive protein. (Table 7.9). However, although there is a similar protective effect conferred by free oestradiol the values do not reach significance when examined per se, or after controlling for age, BMI and C-reactive protein.

Table 7.9 Estimates of risk from logistic regression

Hormone	**Time**	**Odds ratio (95%CI)**		
		unadjusted	***adjusted for age***	***adjusted for C-reactive protein***
Oestradiol (per pmol/l)	Initial	1.01 (1.0, 1.01)	1.01 (1.0, 1.02)	1.0 (0.99, 1.02)
	6 months	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.98 (0.97, 0.99)
Free oestradiol (per nmol/l)	Initial	11.6 (2.71, 49.7)	10.6 (2.3, 47.9)	1.8 (0.03, 122.3)
	6 months	0.42 (0.04, 5.00)	0.43 (0.04, 5.20)	0.34 (0.02, 6.1)

Odds ratio and 95% confidence intervals are shown
The analysis is based on measurements both at baseline and at 6 months. Results show raw data; after adjusting for age and C-reactive protein

7.5 CONCLUSION

Both total and free oestradiol are present in measurable quantities in the serum of elderly men using conventional immunoassays. Levels are within the normal range established for younger healthy men aged between 20-50 years. Levels of both the total and free form of the hormone correlate well with acute phase reactants namely C-reactive protein and serum

albumin. Levels of male sex hormones (free androgen index and testosterone) account for 40% of the variance in free oestradiol levels in addition to age and serum albumin.

Immediately after fracture a significant elevation in levels of both total and free oestradiol is seen. A reduction is seen at 6 months with levels of free oestradiol equalling those in the controls. This is accompanied by significant alterations in levels of acute phase reactants namely C-reactive protein and albumin. Similar findings have been reported after stress conditions like burns and may explain our observations.

Serum oestradiol plays a significant role in determining bone mineral density at all sites. Its influence on BMD is stronger than male sex hormones. Together with free androgen index, past history of fractures and family history of osteoporosis, free oestradiol accounts for 27% of variation in BMD at the femoral neck. Similarly with age, weight and past history of fractures free oestradiol account for 25% of variance in BMD at the lumbar spine.

This study was not designed to explore the relationship between serum oestradiol and risk of hip fracture in men. However, using data at 6 months both total and free oestradiol confer protection although the level of protection conferred by free oestradiol does not reach statistical significance.

8. BONE PROFILE AND CALCIOTROPIC HORMONES

8.1 Summary

This chapter initially evaluates calciotropic hormones (vitamin D and parathyroid) in a randomly selected population of elderly men. It then compares the findings with a matched hip fracture population. Finally, it studies the effects of hip fracture on the bone (calcium, phosphate, and alkaline phosphatase) and calciotropic hormone profile over 6 months and examines their role as risk factors for hip fracture.

In fracture cases and community controls 25-OH-D deficiency was subclinical and existed in the presence of a normal bone profile. No subject had biochemical evidence of osteomalacia. Sixty-five percent cases and 14% controls were confirmed to have 25-OH-D deficiency when first seen. Subjects at most risk of 25-OH-D deficiency were the very elderly, those living alone or in institutions, dependant for basic activities of daily living and spending little time out of doors. It was commoner in men with a cervical fracture than those with an inter-trochanteric fracture. 25-OH-D deficiency persisted 6 months after the fracture despite hospitalisation and being cared for post-operatively in residential and nursing homes. As expected, following fracture alkaline phosphatase levels were significantly raised. They normalised by 6 months.

Using logistic regression and after correcting for age, presence of vitamin D deficiency (<10ng/ml) increased the risk of hip fracture over 10 fold (OR 10.23, 95%CI 5.01, 20.92). Parathyroid hormone levels and urine calcium/creatinine neither conferred risk nor protection to occurrence of hip fracture.

This chapter raises awareness about the magnitude of 25-OH-D deficiency that is prevalent in an elderly Caucasian male community and amongst those presenting with a hip fracture. Therapeutic intervention should be targeted towards the "high risk group" namely, the very elderly who live alone or in institutions and are dependant for normal activities of daily living. This will help reduce the burden of this potentially preventable condition. Persistence of the deficiency state upto 6 months after the fracture furthermore highlights our ignorance and the absence of risk management strategies to identify these potentially reversible deficiency states even amongst hospitalised elderly.

8.2 Background

Long lasting and severe vitamin D deficiency leads to osteomalacia, characterised by typical biochemical abnormalities of low calcium and phosphate and increased activity of alkaline phosphatase. In contrast, patients with primary osteoporosis usually have serum concentrations of calcium and phosphate within the normal range, and alkaline phosphatase rarely elevated. Therefore, in the opinion of many vitamin D deficiency is not an important pathogenetic factor in the development of osteoporosis.

While osteomalacia appears to be uncommon in the majority of patients with hip fracture, subclinical vitamin D deficiency may often promote hip fracture by leading to secondary hyperparathyroidism which in turn increases bone turnover and accelerates bone loss (Chapuy *et al,* 1992, Lips *et al,* 1987). Contrary to the wealth of information on women with hip fractures, the relative importance of vitamin D deficiency as a risk factor for low trauma hip fractures is men is under-recognised. Among the mechanism of bone loss in elderly women, particularly many years after menopause, vitamin D deficiency is probably the most important (Alevizaki *et al,* 1973). Published reports concerning parathyroid levels in patients with hip fracture compared with controls groups are also conflicting (Benhamou *et al,* 1995; MacDonald *et al,* 1992; Cooper *et al,* 1989; Compston *et al,* 1989). However, growing evidence demonstrates that moderately low levels of vitamin D can have unfavourable effects on calcium homeostasis leading to bone loss, even if osteomalacia is not present. Furthermore, supplementation studies with calcium and vitamin D have shown reduction in hip fracture risk in elderly women (Chapuy *et al,* 1992).

The relative importance of vitamin D deficiency, secondary hyperparathyroidism and bone mineral density as risk factors for hip fracture in men is not definitely established. In the framework of a case-control study of risk factors for hip fractures this study aimed to

i) Determine the bone and calciotropic hormone profile of a group of elderly community dwelling men

ii) Compare the findings amongst controls to matched cases with a low trauma hip fracture

iii) Determine effects of hip fracture on serum levels of these hormones, and

iv) Determine the role of calciotropic hormones as risk factors for low trauma hip fracture in elderly men

8.3 Methods

Study design, criteria for inclusion and method of recruitment of cases and controls is detailed in chapter 2. Details of assays used are also given. All laboratory work-up was carried out on blood and urine samples collected early morning after an overnight fast.

Timing: In cases, all samples were collected within 48 hours of fracture. In both groups 25-hydroxyvitamin D, parathyroid hormone, corrected calcium, phosphate and alkaline phosphatase were measured at baseline and at 6 months.

Assays used: 25-hydroxyvitamin D (25-OH D) was measured using the radioimmunoassay (RIA) method with a sensitivity of less than 3ng/ml and coefficient of variation (CV) less than 10%. Parathyroid hormone was assayed using the Nichols Institute Diagnostics intact PTH immunoassay with a CV of <3.4%. Second morning urine after an overnight fast was collected to measure urine calcium. Blood was drawn at the same time to estimate serum creatinine. The urine calcium creatinine ratio was calculated based on these observations.

Vitamin D "deficiency" was defined as serum 25-OH-D levels less than 10ng/ml; vitamin D "insufficiency" was defined as levels less than 20ng/ml. Hyperparathyroidism was defined as serum parathyroid levels greater than 65pg/ml.

Statistical analysis: Descriptive statistics were used to describe individual subject characteristics in both cases and controls. Univariate statistics, both parametric and non-parametric where appropriate were used to compare baseline characteristics between groups. Paired tests were used to determine change in subject characteristics with time between groups. Logistic regression was used to explore the relationship between hip fracture and the putative risk factor. Analysis was adjusted for age, where indicated.

8.4 Results

8.4.1 Calciotropic hormones in community dwelling controls

Subject characteristics and details of laboratory parameters are shown in Table 8.1. Samples of one subject were accidentally discarded in the laboratory before bone profile and urine calcium / creatinine were assayed. Mean levels for all variables were within the normal reference range of the laboratory.

Table 8.1 Bone profile and calciotropic hormones in controls

Variable	*Normal values*	No	Mean	S Dev
Age (yrs)	-	100	75.1	9.6
S Albumin (g/l)	*36-52*	99	43.5	2.9
Corrected Calcium(mmol/l)	*2.1-2.6*	99	2.3	0.08
Inorg Phosphate(mmol/l)	*0.6-1.5*	99	1.0	0.20
Alkaline Phosphatase (IU/l)	*50-120*	99	95.9	38.3
Vitamin D (ng/ml)	*10-42*	100	18.3	7.1
Parathyroid (pg/ml)	*10-65*	100	40.8	21.2
U calcium / creatinine	*100-450*	99	336.4	213.3

At 6 months (n=92): Vitamin D 20.8 ng/ml, Parathyroid 38.1 pg/ml

Sixty percent of the controls had 25-hydroxyvitamin D "insufficiency" (levels <20ng/ml) at baseline. "Deficiency" of 25-hydroxyvitamin D (levels <10ng/ml) was present in 14% (Table 8.2). Seventy nine percent (11/14) of those found 25-hydroxyvitamin D deficient were aged over 70 years. None of the subjects had biochemical features suggestive of osteomalacia.

Table 8.2 Number (%) of controls with low 25-OH-D by decade

Age in decade			**50-59**	**60-69**	**70-79**	**80-89**	**90+**
No per decade			*n=8*	*n=17*	*n=43*	*n=29*	*n=3*
	Levels	*Total*			*n (%)*		
Vitamin D	***<10ng/ml***	***14***	1 (12.5)	2 (11.8)	4 (9.3)	6 (20.7)	1 (33.3)
Vitamin D	***<20ng/ml***	***60***	4 (50)	10 (58.8)	28 (65.1)	16 (55.2)	2 (66.7)
Parathyroid	***>65 pg/ml***	***8***	-	-	3 (7)	4 (13.8)	1 (33.3)
Urine Ca/Cr	***<100***	***24***	1 (12.5)	5 (29.4)	13 (30.2)	5 (17.2)	-
Urine Ca/Cr	***>100***	***7***	2 (25)	-	4 (9.3)	1 (3.4)	-

25-OH-D deficiency was significantly more common in those institutionalised (living in nursing and residential homes) than those living in their own home: 75% versus 12% respectively, χ^2 =15.6, df=3, p<0.001. Amongst those living at home, it was commoner in those living alone [3/16 (18.8%)] than those with family [8/78 (10.3%)]. In addition, it was significantly more common in those single or widowed [6/21 (28.6%)] than those married living with spouse [8/79 (10.1%), χ^2 =4.7, df=1, p<0.03]. It was commoner in those less ambulant and spending less than one hour walking out of doors each day compared to those who walked one hour or more (12/ 59 (20.3%) & 2/41 (4.9%) respectively χ^2 = 4.8, df=1, p<0.03).

25-OH-D insufficiency (levels <20ng/ml) was commoner in those who walked less than an hour out of doors [38/59 (64.4%)] compared to those who spent more than an hour each day [22/41 (53.7%)]. The latter did not reach statistical significance. All 4 (100%) living in care had 25-hydroxyvitamin D insufficiency (levels <20ng/ml).

Hyperparathyroidism was present in 8(8%) of controls; all were aged 70 years and over. Only 3% had both low vitamin D (<10ng/ml) and elevated PTH (>65ng/ml). Low urine calcium creatinine ratio (<100mmol/mmol) was present in 7/99 (7.1%). Nine (9%) had a combination of low 25-OH-D, raised parathyroid and low urine calcium / creatinine.

Table 8.3 shows the change in bone and calciotropic hormone profile with age. There was a modest correlation between age and parathyroid hormone (r_s=0.41; p<0.01; n=100); a small but significant correlation with corrected calcium (r_s=0.25; p<0.05; n=99) but none with 25-OH-D levels. There was no correlation between age and serum albumin, alkaline phosphatase, inorganic phosphate and urine calcium creatinine ratio.

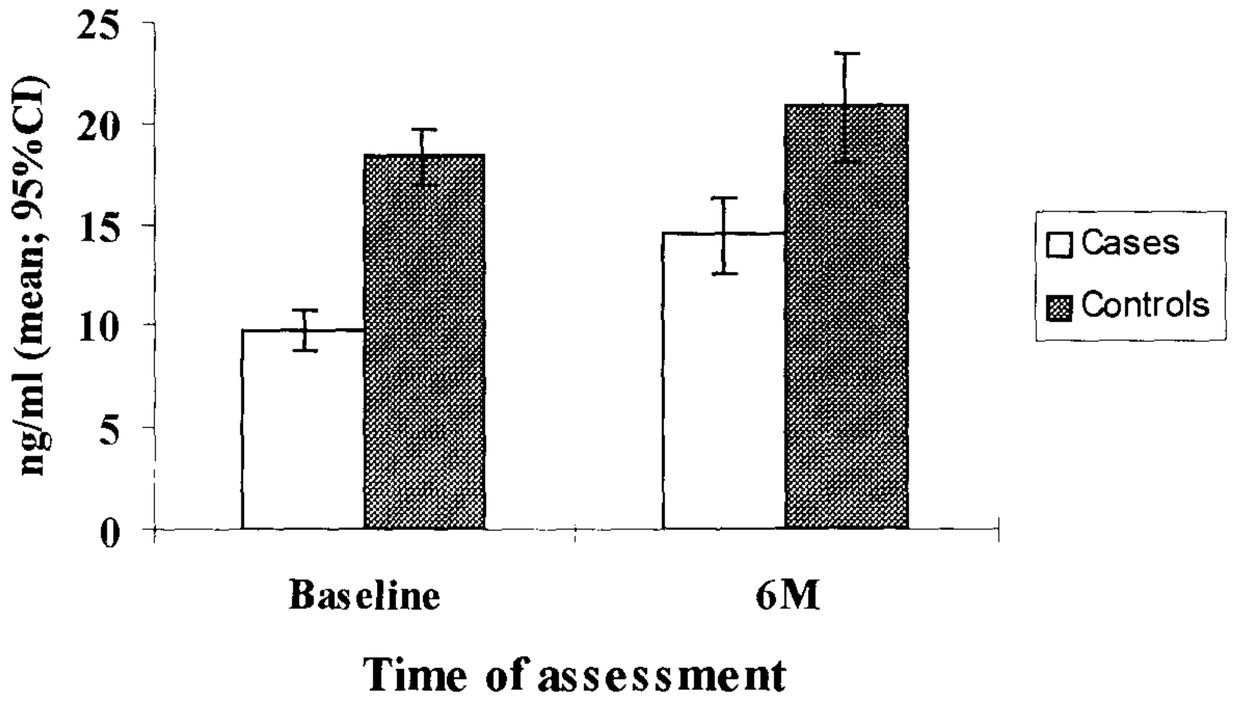
There was no correlation between 25-hydroxyvitamin D levels, body mass index, parathyroid hormones, bone markers and BMD at any site (data not shown). A weak but significant correlation was seen between 25-OH-D levels and urine calcium creatinine ratio r_s=0.21; p<0.05; n=99.

Table 8.3 Change in bone profile with age amongst controls (mean & S Dev)

Age in decade	50-59	60-69	70-79	80-89	90+
No per decade	*n=8*	*n=17*	*n=43*	*n=29*	*n=3*
Age (yrs)	54.1 (3.3)	67.5 (1.6)	74.1 (2.7)	84.8 (2.3)	95 (2)
S Albumin (g/l)	42.1 (3.8)	44.9 (2.7)	43.1 (2.8)	43.4 (3)	43.7 (0.6)
Corrected Calcium(mmol/l)	2.3 (.05)	2.3 (.08)	2.3 (.09)	2.3 (.07)	2.4 (.05)
Inorganic phosphate(mmol/l)	1.1 (0.2)	1.1 (0.3)	1.0 (0.2)	1.0 (0.1)	1.2 (0.2)
Alkaline Phosphatase (IU/l)	80.4 (25.5)	94.4 (36.6)	89 (22)	116 (55.8)	98 (33.90
Vitamin D (ng/ml)	21.5 (8.4)	18.0 (6.1)	18.4 (7.1)	18 (7.3)	15 (8.4)
Parathyroid Hormone (pg/ml)	25.6 (11.3)	35.5 (10.40	38.1 (16.6)	49.4 (28.2)	66.7 (26.3)
U calcium / creatinine	264.6 (260.8)	400.1 (227.7)	361.5 (238.7)	293.1 (134.8)	171.5 (71.4)

An increase in 25-hydroxyvitamin D levels was noted at 6 months (Figure 8.1). Fifty six of the 92 controls tested at both time points showed an increase (Wilcoxon Signed Ranks test $p<0.003$). This was statistically but not clinically significant. (25-hydroxyvitamin D level 18.3 ng/ml at baseline; 20.7 ng/ml at 6 months). No significant change was observed in other laboratory variables including parathyroid hormone over the 6-month period.

Figure 8.1 25-hydroxyvitamin D in cases and controls at baseline and at 6 month



8.4.2 Bone profile and calciotropic hormones in men with hip fracture

It was possible to collect fasting early morning blood samples in 95 cases within 48 hours of the fracture. Catheterization made it difficult to collect appropriate urine samples for calcium estimation in all cases.

Within 48 hours of the fracture, serum albumin and 25-OH-D level were low while alkaline phosphatase was near the upper limit of the reference range of the laboratory (Table 8.4). A significant increase in 25-hydroxyvitamin D levels was noted at 6 months (see footnote table 8.4). Thirty six of the 50 cases who had measurements at both time points showed an increase (Wilcoxon Signed Ranks paired t test $p<0.01$). This rise (9.7ng/ml at baseline; 14.4 ng/ml at 6 month) was clinically significant.

A significant increase was also seen in levels of urine calcium/creatinine 6 months after the fracture. Twenty-seven of the 40 cases tested at both time points showed an increase (Wilcoxon Signed Ranks paired t test, $p<0.02$). The decrease in parathyroid hormone levels from 47.1 pg/ml at baseline to 43.2 pg/ml at 6 months was not significant (Wilcoxon Signed Ranks paired t test, p=NS). There was no significant change in other variables namely albumin, alkaline phosphate, phosphate and calcium.

Table 8.4 Bone profile and calciotropic hormones in men with hip fracture (Mean & SDev are shown)

Variable	*No*	Normal values	Cases
Age(yrs)	*100*	-	79.9(9.4)
S Albumin(g/l)	*95*	36-52	33.8(4.8)
Co Calcium(mmol/l)	*94*	2.1-2.6	2.3(0.1)
In Phosphate(mmol/l)	*90*	0.6-1.5	1.1(0.3)
Alk Phosphatase(IU/l)	*94*	50-120	116.9(69.6)
25-OH-D(ng/ml)	*94*	10-42	9.7(4.7)
Parathyroid(pg/l)	*95*	10-65	47.1 (31)
U calcium / creatinine	*81*	100-450	278.4(226.1)

At 6 months (n=51): Vitamin D 14.4 ng/ml; Parathyroid hormone 43.2 pg/ml

25-OH-D levels were similar in cases with a cervical fracture and those with an inter - trochanteric fracture [mean (SD) cervical fracture: 9.2(4.2) ng/ml; inter trochanteric: 10.4(5.3) ng/ml; p=NS]. However, 25-OH-D deficiency (< 10ng/ml) was commoner in subjects with a cervical fracture (70.6%) than those with an inter trochanteric fracture (58.1%) χ^2=1.6; p=NS). 25-OH-D deficiency was commoner in those who were either single, widowed or divorced compared to those married [30/43 (69.8%) Vs 31/51(60.8%) χ^2=0.83; p=NS]. No difference were seen in their residential status (home versus in care) and degree of mobility (walking less than or more than an hour out of doors most days).

Elevated PTH (>65pg/ml) was present in 17(17.9%) fracture cases; 16(94%) were aged over 70 and 14(82%) had additional low 25-OH-D. Low urine calcium/creatinine (<100 mmol/mmol) was seen in 23 (28.4%) cases.

8.4.3 Comparison between hip fracture cases and community controls

Hip fracture cases were significantly older compared to community controls (p<0.01) Table 8.5. Of the variables under study only age correlated to parathyroid hormone (r_s=0.41; p<0.01). Hence, age adjustment (see "*" Table 8.5) was carried when comparing parathyroid levels between the two groups. Albumin, inorganic phosphate and 25-OH-D were significantly lower in cases compared to controls (Table 8.5). Alkaline phosphatase was significantly elevated in cases compared to controls (p<0.01).

Table 8.5 Differences in cases and controls at baseline (mean & SD are shown)

Variable	*Normal values*	Cases	Controls	Significance
Age(yrs)	-	79.9(9.4)	75.1(9.6)	0.01
Albumin(g/l)	*36-52*	33.8(4.8)	43.5(2.9)	0.01
Co Calcium(mmol/l)	*2.1-2.6*	2.3(0.1)	2.3(0.1)	NS
Phosphate(mmol/l)	*0.6-1.5*	1.1(0.3)	1.0(0.2)	0.04
Alk Phosphatase(IU/l)	*50-120*	116.9(69.6)	95.9(38.3)	0.01
25-OH-D(ng/ml)	*10-42*	9.7(4.7)	18.3(7.1)	0.01
Parathyroid(pg/l)	*10-65*	47.1 (31)	40.8 (21.2)	NS
Parathyroid *		42.0 929)	40.8 (21.2)	NS
U calcium / creatinine	*100-450*	278.4(226.1)	336.4 (213.3)	NS

Using the definitions described earlier 65% cases had vitamin D "deficiency" compared to 14% controls (OR 11.4; 95%CI 5.6, 23) see Table 8.6. Vitamin D "insufficiency" was seen in 97% cases compared to 60% controls (OR 20.2; 95%CI 5.9, 68.3). Hyperparathyroidism was found in 18% cases compared to 8% controls (OR 2.5; 95%CI 1.0, 6.1). 14.9% of cases had both 25-hydroxyvitamin D deficiency and hyperparathyroidism compared to only 3% of controls. Low urine calcium/creatinine was seen in 23/81 (28.4%) cases compared to 7/99 (7.1%) controls (OR 5.2; 95%CI 2.1, 12.9)

Table 8.6 Odds ratios for low 25-OH-D, raised PTH and low U Ca/Cr at baseline

	Cases	**Controls**			
Abnormal values	***No (%)***	***No (%)***	***Odds ratio***	***Chi-square***	***Sig***
Vit D <20 ng/ml	91 (96.8)	60 (60)	20.2	38.1	<0.01
Vit D <10 ng/ml	61 (64.9)	14 (14)	11.4	52.9	<0.01
PTH >65 ng/ml	17 (17.8)	8 (8)	2.5	4.3	<0.04
U Ca/Cr <100	23 (28.4)	7 (7.1)	2.1	14.6	<0.01

8.4.4 Calciotropic hormones as risk factors for hip fracture

After correcting for age and using logistic regression analysis, per nanogram (ng) increase in vitamin D reduced the risk of hip fracture by 20% (OR 0.79, 95%CI 0.73, 0.85). Vitamin D sufficiency (>10ng/ml) reduced the risk by more than 90% (OR 0.1; 95% CI 0.05, 0.20). Parathyroid hormone levels and urine calcium/creatinine neither conferred risk nor protection to occurrence of hip fracture.

8.5 Conclusion

Low 25-OH vitamin D was common in hip fracture patients, who in addition were old, living alone at home or in institutions, incapable of independent daily life and spent insufficient time out of doors. Low 25-OH-D levels were present in the presence of a normal bone profile absence of raised parathyroid levels and, biochemical picture suggestive of osteomalacia. The 25-OH-D deficiency state was subclinical and emphasises the frailer condition of hospitalised patients with hip fracture. Low 25-OH-D levels have previously

been reported in hip fracture patients when compared with healthy controls (Chapuy *et al,* 1992; Lips *et al,* 1987; Cooper *et al,* 1989).

A significant increase in 25-OH-D levels were noted 6 months after the hip fracture compared to measurements in the immediate post fracture state. An explanation for this observation may be the timing of sampling after fracture (Ng *et al,* 1994) and/or nutrition supplements in hospital and in institutions following admission.

Hyperparathyroidism was present in 18% of men with hip fracture compared to 8% of men living in community. The presence of secondary hyperparathyroidism in elderly people has previously been suggested, especially in patients with hip fracture (Benhamou *et al,* 1994; Compston *et al,* 1989). In this study parathyroid levels were similar in the two groups throughout the study duration. Published literature is conflicting with some studies even reporting *lower* levels of parathyroid hormone in the face of low 25-OH-D levels in both men and women with hip fracture compared to controls (Thieuband *et al,* 1997). Alteration in serum chemistry following fracture may be account for these differences. This calls for caution in interpreting biochemical data in elderly patients who have recently sustained a hip fracture.

14% of the elderly Cornish men living in community also exhibited 25-OH-D deficiency. This was most marked in those in institutions or living alone at home and less ambulant. Similar results have been reported in recent years from the continent - 14% in an adult urban French population (Chapuy *et al,* 1992) and 6% among Swiss adults (Burnand *et al,* 1992). The authors relate vitamin D levels to latitude of residence and hours of sunshine. In contrast, men in North America have been shown to have a very low prevalence of vitamin D deficiency (Gallagher *et al,* 1998). An explanation for this difference is better sunlight exposure coupled with supplementation of dairy produce in the USA.

Results from this study in combination with those published earlier highlight the common problem of vitamin D deficiency with resultant sub-optimal calcium absorption in the "healthy" elderly men living in community. It also underlines the even higher prevalence of vitamin D deficiency in men with hip fracture. Simple measures to replenish the deficiency status in these men will go a long way in fracture prevention.

9. BONE MARKERS

9.1 SUMMARY

This chapter addresses a number of issues. Firstly, it looks into the question whether elderly men with hip fracture have a different bone turnover as compared to healthy men of the same age. Subsequently, it looks into differences in bone metabolism between men with cervical and inter-trochanteric hip fracture. Finally, it throws insight into the process of bone remodelling in a group of elderly men living in the community over a 6-month period.

The subjects studied are those detailed in chapter 2. Baseline blood and second-morning void urine samples were collected shortly after fracture (maximum 48 hours) and, at the time of the first visit in controls. Repeat samples, in both groups, were collected at 6 months.

In men with hip fracture there was impairment of bone turnover evident by reduced bone formation with elevated bone resorption. This may account for net bone loss and susceptibility to fracture. There was no correlation between levels of bone markers and acute phase reactants (albumin, CRP, cortisol), suggesting this uncoupling to be antedating the fracture event. At 6 months both markers were elevated suggesting increased bone turnover associated with fracture healing. No measurable differences were noted in bone markers between men with cervical and inter-trochanteric hip fracture.

In contrast, amongst controls, both osteocalcin and urinary deoxypyridinoline were within the normal reference range, suggesting normal bone remodelling. This was seen both at the time of the first visit and at 6 months. However, rate of bone turnover significantly declined within the group over this 6-month period. This was evident by significant reduction in both bone markers over this period. One explanation may be change in lifestyle and diet secondary to education as a result of participation in the study.

The study was not designed to address the role of bone markers as risk factors for hip fracture. Within this constraint, this study shows a 40% increase in the risk of hip fracture (OR 1.41, 95%CI 1.3, 1.6) per unit increase in urinary deoxypyridinoline, and, an 18% reduction in risk of hip fracture per ng/ml increase in serum osteocalcin (OR 0.82, 95%CI 0.73, 0.92). This risk / protection conferred is not altered after adjusting for age or BMD.

9.2 BACKGROUND

Bone loss and increased bone turnover are recognised local changes after a fracture, but the exact pattern of these changes after different types of fracture is unclear. The availability of biochemical markers of bone metabolism enables us to study the different states of bone turnover.

Biochemical markers of bone turnover are increased after fracture in some studies (Ingle *et al,* 1999; Bowles *et al,* 1997; Nyman *et al,* 1991) but not all (Lauritzen *et al,* 1987). In elderly osteoporotic subjects sustaining hip fracture, both increased (Slovik *et al,* 1984) and decreased (Cooper *et al,* 1989, Akesson *et al,* 1993) osteocalcin levels have been noted. The variations in the levels of bone markers may reflect, either the general underlying bone metabolic alterations caused by the disease, or post-traumatically induced changes related to the fracture event or the callus formation. Except for the study by Akesson in women with hip fracture (Akesson *et al,* 1993), measurements have been performed in a limited number of patients, and, in most cases, several days to weeks after the hip fracture.

Abnormalities of bone turnover responsible for bone loss in men with osteoporotic fractures have not been clearly defined. With the increasing use of biochemical markers of bone turnover in the study of osteoporosis, it is important that the effects of fracture and fracture healing on levels of these markers are better understood.

The aim of this study was to analyse potential abnormalities of bone turnover in elderly men shortly after hip fracture. To evaluate the bone metabolism status of these men, serum osteocalcin was used as a marker of bone formation and urinary deoxypyridinoline to reflect bone resorption. Subsequently, comparisons were made with matched controls without hip fracture. In order to avoid the confounding effects of fracture per se on bone turnover, samples were drawn as close to occurrence of hip fracture as possible (usually within 24 hours, maximum 48 hours). Furthermore, levels of bone markers in serum were correlated with acute phase proteins and repeat measurements carried out at 6 months. Follow-up at 6 months also helped evaluate bone metabolic properties during the phase of fracture healing. In addition, an attempt was made to address differences in bone metabolism between men with cervical and intertrochanteric hip fracture.

9.3 PATIENTS AND METHODS

9.3.1 Study Design

100 men, admitted consecutively with a low trauma hip fracture over a 14-month period were identified as cases. An equal number of men were randomly recruited as controls from a local general practice register. Details of the study design are given in chapter 2.

9.3.2 Measurement Of Biochemical Markers Of Bone Turnover

Bone markers were assayed at baseline (within 48 hours in men with hip fracture and at the time of the first visit in controls) and at 6 months. Majority of the initial measurements were made prior to fluid substitution and surgery. An early morning fasting blood sample and a 2-hour second morning urine sample were collected, for serum osteocalcin and urinary deoxypyridinoline, respectively. Blood samples were centrifuged immediately after collection and serum separated. Aliquots of serum and urine were stored at -80° C until assay. Samples collected from individual subjects were measured within a single analytical batch. The within batch CV was calculated from analytical duplicates for each analyte, details of which are in chapter 2.

Osteocalcin was used as the marker for bone formation and urine deoxypyridinoline for bone resorption. Intact osteocalcin was assayed in serum using NovoCalcinTM kit. The assay has a minimum detection limit of 0.45 ng/ml. The intra assay and inter assay CVs over the range 6.2-16.5 ng/ml were <10 and <9.8% respectively. Deoxypyridinoline cross-links were measured in the second-morning void urine using Pyrilinks-D immunoassay by Metra Biosystems. The assay is sensitive to detect a minimum value of 1.1 nmol/l. The within and between -run CV of the assay at the range <5.4 Dpd values is 8.4% and 4.8%, respectively.

9.3.3 Analysis

Descriptive statistics were used to describe group characteristics in both cases and controls. Univariate statistics, both parametric and non-parametric where appropriate, were used to compare baseline values between groups. Paired tests were used to determine change over time. Logistic regression was used to explore the relationship between hip fracture and the putative risk factor i.e. bone markers. Age adjustments were made in calculating odds ratio using STATA.

9.4 RESULTS

9.4.1 Bone markers in controls

The number of subjects where measurements of various bone markers was possible at the two time intervals is given in Table 9.1. Osteocalcin was measured in only 71 men at baseline and in 92 at 6 months. The large number of missing observations, at baseline, was a result of the samples being misplaced in the laboratory.

Table 9.1 Bone markers in controls at baseline and at 6M (Mean & SD are shown)

Variable	N range	*Time*	No.	Mean	SD	P*
Age (years)		***Baseline***	100	75.1	9.6	
Osteocalcin (ng/ml)	3.4-9.1	***Baseline***	71	8.3	6.2	
		6M	92	6.2	4.1	<0.0001
U D-Pyr(nM/nM)	2.3-5.4	***Baseline***	96	5.5	3.5	
		6M	90	5.1	2.6	<0.04
Alkaline Phos (IU/l)	50-120	***Baseline***	99	95.9	38.3	NS
		6M	90	98.4	41.3	

* Wilcoxon signed rank test between baseline and 6 months

Serum osteocalcin and urinary deoxypyridinoline were within the normal range of the laboratory both at baseline and at 6 months (Table 9.1). A decrease in levels of both bone markers was seen at 6 months. Of the 86 controls who had measurements both at baseline and at 6 months, 50 showed a decrease in urinary deoxypyridinoline. Similarly, of the 68 controls, 54 showed a decrease in serum osteocalcin. This decrease in both markers over the 6 month period was statistically significant (Wilcoxon signed ranks test, $p<0.04$ & $p<0.0001$ respectively (Table 9.1).

Osteocalcin and urinary deoxypyridinoline had a modest correlation with each other (r_s =0.36, n=69, $p<0.01$), but not with alkaline phosphatase. Osteocalcin also correlated with age (OC: r_s =0.24, n=71, $p<0.05$; Udpd: r_s =0.18, n=96, p=NS; AlkPhos: r_s =0.13, n=99,

p=NS). In the very elderly (over 80 years) both osteocalcin and urinary deoxypyridinoline were above the laboratories normal range suggesting high bone turnover (Table 9.2). Urinary deoxypyridinoline had a small but significant inverse relationship with femoral neck BMD (r_s =-0.21, n=96, p<0.05). There was no correlation with BMD at any other site. No correlation was found between BMD, osteocalcin and alkaline phosphatase. Only alkaline phosphatase correlated with CRP (r_s = 0.20, n=99, p<0.04).

Table 9.2 Change in bone markers in controls with age (Mean & SD are shown)

Variable	***N range***	***50-59***	**60-69**	**70-79**	**80-89**	**90+**
No.		***8***	***17***	***43***	***29***	***3***
Age (years)		54.1 (3.3)	67.5 (1.6)	74.1 (2.7)	84.8 (2.3)	95 (2)
Osteocalcin (ng/ml)	***3.4-9.1***	6 (1.4)	7.4 (3.3)	6.3 (2.1)	11.4 (9.6)	14.2 (8.9)
U D-Pyr(nM/nM)	***2.3-5.4***	5.3 (2.2)	5.2 (2.1)	4.5 (1.7)	6.6 (5)	11.6 (5.6)
Alkaline Phos (IU/l)	***50-120***	80.4 (25.5)	94.4 (36.6)	89 (21.9)	111.6 (55.8)	98 (33.9)

High urinary deoxypyridinoline defined as levels more than 5.4 nM/nM was present in 38/96 (39.6%) controls at baseline and in 25/90 (27.8%) at 6 months (Table 9.3). 20 of the 38 men (52.6%) at baseline and 15 of the 25 (60%) at 6 months were over the age of 80.

Table 9.3 Subjects with abnormal bone markers at baseline and at 6 months Number (%) are shown

		Cases	**Controls**
Abnormal values		***No (%)***	***No (%)***
U. D-Pyridinoline >5.4	*Baseline*	78 (86.7)	38 (39.6)
	6 Months	38 (77.6)	25 (27.8)
S Osteocalcin <3.4	*Baseline*	16 (16.8)	3 (4.2)
	6 Months	4 (7.8)	21 (22.8)
U dpd>5.4 & Osteo >9.1	*Baseline*	8 (8.9)	10 (14.4)
	6 Months	17 (34.6)	7 (7.8)

9.4.2 Bone markers in men with hip fracture

Serum osteocalcin was measured in 95 cases within 48 hours of the hip fracture and in 51 of the survivors at 6 months. 52 fractures were cervical and 43 were inter-trochanteric. Urine for deoxypyridinoline was collected in 90 and 49 cases at baseline and 6 months, respectively. Similarly, serum alkaline phosphatase was measured in 94 and 51 cases respectively (Table 9.4).

Following fracture, C-reactive protein showed a significant increase in hip fracture patients compared to controls (Cases: 120.5 mg/l; controls: 3.0 mg/l; $p<0.01$). Concomitantly, serum albumin levels were 22.3% lower in men with hip fracture as compared to controls. Serum cortisol levels were markedly raised [mean (SD): 630.8mIU/l (266.1)]. Co-morbid diseases were significantly more common in cases compared to controls (for details see chapter 3).

Serum osteocalcin levels on admission were 32.5% lower in men with hip fracture as compared to healthy controls (cases: 5.6 ng/ml; controls: 8.3 ng/ml; $p<0.01$). In men with hip fracture, at follow-up 6 months later, serum osteocalcin levels had significantly increased (46.4%) and reached levels 32.2% higher than the controls (cases: 8.2 ng/ml; controls: 6.2 ng/ml; $p<0.04$). Of the 50 fracture cases that had measurements both at baseline and at 6 months, 31 (62%) showed an increase in serum levels of osteocalcin compared to baseline. This increase was statistically significant (Wilcoxon signed ranks test; $p<0.009$).

Soon after the hip fracture (within 48 hours), alkaline phosphatase was significantly elevated in cases compared to controls (cases: 116.9 IU/l; controls: 95.9 IU/l; $p<0.01$). In parallel to the changes observed in serum osteocalcin, the further rise in serum alkaline phosphatase levels, 6 months later, was significant but less marked (6.9%). 33 of the 51 cases who had measurements carried out at both time points showed an increase (Wilcoxon signed ranks test $p<0.009$) see Table 9.4.

At the time of the hip fracture, urinary deoxypyridinoline was more than two times the value in the controls (cases: 11.2, controls: 5.5; $p<0.01$). These elevated levels persisted amongst the survivors' 6 months after the fracture (Table 9.4). Of the 47 fracture cases who had measurements both at the time of the hip fracture and at 6 months, 27 (57.4%) showed a

further increase in urinary deoxypyridinoline at 6 months. This did not reach statistical significance.

Table 9.4 Differences between cases and controls: baseline & at 6 months (Mean & SD are shown)

Variable	N range	*Time*	Cases		Controls		*Sig*
			No.	*Mean (SD)*	*No.*	*Mean (SD)*	*Mann Whitney*
Age (years)			100	79.9 (9.4)	100	75.1 (9.6)	<0.01
C-reactive protein (mg/l)	0-10		82	120.5 (76.4)	100	3.0 (5.4)	<0.0001
S Albumin (g/l)	36-52	*Baseline*	95	33.8 (5.0)	99	43.5 (2.9)	<0.0001
Cortisol (mIU/l)	105-525	*Baseline*	89	630.8 (266)		NT*	
Osteocalcin (ng/ml)	3.4-9.1	*Baseline*	95	5.6 (2.7)	71	8.3 (6.2)	<0.0001
		6M	51	8.2 (5.3)	92	6.2 (4.1)	<0.04
U D-Pyr(nM/nM)	2.3-5.4	*Baseline*	90	11.2 (6.1)	96	5.5 (3.5)	<0.0001
		6M	49	10.2 (5.7)	90	5.1 (2.6)	<0.0001
Alkaline Phosphatase (IU/l)	50-120	*Baseline*	94	116.9 (69.6)	99	95.9 (38.3)	<0.01
		6M	51	125 (52.6)	90	98.4 (41.3)	<0.01

* NT: Not tested

Men with hip fracture exhibited an imbalance of bone turnover with depressed bone formation and higher bone resorption. At the time of the hip fracture, poor bone formation exemplified by low serum osteocalcin (<3.4 ng/ml) was present in 16/95 (16.8%) cases. In contrast, increased bone loss suggested by high urinary deoxypyridinoline, defined as levels more than 5.4 nM/nM, was present in 78/90 (86.7%) cases (Table 9.3). Six months after fracture, bone turnover was increased with 17 (34.6%) cases exhibiting elevated levels of both serum osteocalcin and urinary deoxypyridinoline (Table 9.3).

Men with cervical fracture were two years older compared to those with fracture at the inter-trochanteric site. There was no measurable difference in bone markers between the two groups (Table 9.5). Similarly, although men with 3 or more co-morbid diseases were older than those not diseased, there were no quantifiable differences in levels of bone marker between the two groups (Table 9.6).

Table 9.5 Bone markers in men with cervical versus inter-trochanteric fracture

	Cervical		Inter-trochanteric		
Variable	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*p*
Age (yrs)	*55*	80.8 (8.9)	*45*	78.9 (9.8)	NS
S Osteocalcin (ng/ml)	*52*	5.8 (3)	*43*	5.3 (2.4)	NS
U D Pyr (nM/nM)	*50*	11.3 (5.5)	*40*	11 (6.8)	NS
Alkaline Phos (IU/l)	*51*	113.6 (57.3)	*43*	120.7 (82.4)	NS

Table 9.6 Bone markers in relation to presence of co-morbidity

	No co-morbidity		3 or more co-morbidities		
Variable	*n*	Mean (SD)	*n*	Mean (SD)	p
Age (yrs)	*21*	78.3 (13.6)	*75*	80.4 (7.9)	NS
C-reactive protein	*18*	103.5 (76.8)	*64*	125.3 (76.2)	NS
S Osteocalcin (ng/ml)	*20*	5.9 (3.4)	*75*	5.5 (2.5)	NS
U D Pyr (nM/nM)	*18*	12.4 (8.0)	*72*	10.9 (5.5)	NS
Alkaline Phos (IU/l)	*20*	126.1 (40.4)	*74*	114.4 (75.6)	NS

As expected, osteocalcin correlated to alkaline phosphatase $r_s = 0.23$ ($p<0.05$). To evaluate whether or not the serum osteocalcin level was only a direct reaction to the sustained fracture, the study addressed the correlation to the acute phase response namely serum albumin, C-reactive protein and cortisol. No correlation was seen between bone markers, and any of the acute phase reactants measured at the same time (Table 9.7). No correlation was seen between bone markers and age or BMD at baseline and at 6 months amongst fracture cases.

Table 9.7 Correlation with age, acute phase reactants and BMD

	Age	Serum Albumin	C-Reactive Protein	Cortisol	BMD (Femoral neck)	BMD (L Spine)
Osteocalcin	0.15	0.01	0.03	-0.02	-0.16	-0.05
U D Pyr	-0.06	-0.24*	0.08	0.15	0.02	-0.13
Alkaline Phos	0.25*	-0.04	-0.04	0.21	-0.26*	-0.12

* $p<0.01$

9.4.3 Bone markers as a risk factor for low trauma hip fracture

Using baseline data, obtained within 48 hours of the event in cases, urinary deoxypyridinoline was a significant risk factor for low trauma hip fracture. There was a 40% increase in the risk of hip fracture (OR 1.41, 95%CI 1.3, 1.6) per unit increase in urinary deoxypyridinoline using multiple logistic regression. This risk was unchanged after adjusting for age (OR 1.38, 95%CI 1.2, 1.6) and or BMD (OR 1.34, 95%CI 1.2, 1.5). Elevated urinary deoxypyridinoline (>5.4) increased the risk of hip fracture 10 fold (OR 9.9) see Table 9.8. The risk associated was unchanged on repeating the analysis using the 6-month data.

Table 9.8 Odds ratios for abnormal bone markers at baseline

	Odds ratio (95%CI)	
Abnormal values	***unadjusted***	***adjusted for age***
U D-Pyridinoline (nM/nM)	1.41 (1.25, 1.58)	1.39 (1.23, 1.56)
S Osteocalcin (ng/ml)	0.82 (0.73, 0.92)	0.77 (0.68, 0.88)
U. D-Pyridinoline >5.4 (nM/nM)	9.92 (4.77, 20.64)	8.95 (4.26, 18.81)
S Osteocalcin >9.1 ng/ml	0.35 (0.15, 0.81)	0.21 (0.08, 0.53)
S Osteocalcin <3.4 ng/ml	4.59 (1.28, 16.43)	4.67 (1.27, 17.16)

Serum osteocalcin is associated with a decreased risk of hip fracture. There was a reduction in risk of hip fracture by 18% per ng/ml increase in serum osteocalcin (OR 0.82, 95%CI 0.73, 0.92). The protection conferred was not altered after adjusting for age (OR 0.77, 95%CI 0.68, 0.88) or BMD (OR 0.76, 95%CI 0.64, 0.90). Serum osteocalcin levels greater than 9.1 ng/ml reduced the risk of hip fracture by two third (OR 0.35) see Table 9.8.

9.5 CONCLUSION

As expected, men aged 50 and over, living in the community exhibit normal bone remodelling. Finding normal levels of serum osteocalcin and urinary deoxypyridinoline in this cohort of men over a 6-month period supports this. However, in the very elderly (over 80 years) there is evidence to suggest a state of increased bone turnover. This is illustrated by significantly elevated levels of both serum osteocalcin and urinary deoxypyridinoline in men in this age group. In addition, one is able to demonstrate a good correlation between

age and osteocalcin. However, this result needs to be interpreted with caution, as the study was limited in the number of subjects studied in this age range.

A statistically significant decrease in both bone markers, implying reduced bone turnover, was observed amongst the controls over the 6-month period. One explanation may be changes in lifestyle habits associated with increased calcium intake by diet or supplements as a result of participation in the study.

This study failed to provide evidence to suggest that the rate of bone turnover determines BMD in elderly men. No relationship was found between BMD and osteocalcin and only a weak relation (r_s=-0.21) with urinary deoxypyridinoline.

It has been proposed that intertrochanteric fractures are the consequence of more severe osteoporosis than cervical hip fractures. In this study, bone markers have not pointed to any difference between these fracture types. On the contrary, similar levels have been found in patients with either fracture type.

The data acquired suggests that bone turnover is disturbed in elderly men sustaining a hip fracture. In contrast to the expected age-related increase of osteocalcin, men with hip fracture instead have reduced osteocalcin level, reflecting decreased bone formation. The lower osteocalcin level in the fracture patients may indicate that this population of elderly men has impaired osteoblast function.

Elderly men with hip fracture have an uncoupling of bone formation and resorption; changes that may contribute to net loss of bone. Significantly elevated levels of urinary deoxypyridinoline at the time of the fracture along with reduced serum osteocalcin supports this hypothesis. The increased resorptive activity seems unrelated to metabolic alterations induced by trauma and surgery. Absence of correlation between both bone markers and acute phase reactants, including cortisol levels at the time of initial sampling, indicates that reduced osteocalcin and urinary deoxypyridinoline are unrelated to the trauma-induced cortisol surge in these patients. Neither does it seem likely that cortisol should have a momentary effect on the osteoblasts and the higher urinary deoxypyridinoline level is not related to cortisol in the study. Furthermore, renal function was not significantly different

between the two groups. Therefore, an impaired kidney function or alteration in creatinine clearance cannot explain the increased urinary deoxypyridinoline.

It has been shown that elderly patients in the presence of co-morbid diseases and poor mobility have increased bone resorption. Fracture patients were more disabled and had significantly more diseases compared to controls. Differences observed in this cohort of patients did not reach statistical significance.

These data suggest that, the abnormal levels of osteocalcin and urinary deoxypyridinoline are unrelated to traumatically induced changes, but reflect abnormal bone turnover prior to fracture. These abnormalities may play a role in the decrease of bone mass and consequently the increased bone fragility that characterises osteoporotic hip fractures in the elderly.

Men with hip fracture are capable of responding adequately to the fracture and initiate the healing process, which is reflected as an increase of both osteocalcin and alkaline phosphatase levels at 6 months. Whether the post fracture metabolic response reflects a general reactive increase of the bone turnover caused by the fracture itself or whether it is explained by fracture healing is debatable.

Within the constraints of the study design, elevated urinary deoxypyridinoline is a risk factor and raised osteocalcin is protective for low trauma hip fracture in men. The risk / protection conferred is independent of age and bone mineral density. High levels of osteocalcin reduce the risk of hip fracture by two third (OR 0.35). Conversely, elevated urinary deoxypyridinoline increase the risk by 10 fold (OR 9.9).

The study has limitations. Ideally, the first samples should be taken before occurrence of the fracture. In this study baseline samples were taken within 48 hours of the event when some changes may have already taken place affecting the true levels of the markers. This would not only alter the strength of the association between bone markers and risk of hip fracture but also raise doubt on the degree of uncoupling observed in these men following the fracture. There are little published data on the response to fracture using biochemical markers, and comparison with other studies is difficult because of different baseline sampling times, a variety of fractures and a number of markers measured by different methods. Another drawback of this study is the accidental loss of a small proportion of samples in the

laboratory. It may be argued that samples lost may have been different from those that were assayed. This is extremely unlikely, as there was no systematic selection bias.

Fracture patients were ill and had significantly more concomitant illnesses like Parkinson's and stroke, which impaired mobility significantly more than the controls. However, no differences in bone markers were found in men with or without co-morbid disease.

The study is limited in allowing us to identify the reasons for the increased bone resorption and its precise relation to occurrence of the fracture. Whatever the temporal profile of the bone resorption process in relation to fracture occurrence, it is evident that bone resorption continues unabated in as high as 77.6% of survivors at 6 months. Translating this in clinical terms, there may be an argument to initiate anti resorptive agents in individuals who sustain a fracture to reduce risk of further fractures.

10. QUALITY OF LIFE AND FUNCTIONAL IMPAIRMENT

10.1 SUMMARY

This chapter addresses the quality of life and functional ability of a group of randomly selected elderly men living in community and compares their health to the standard norms published for the US general population. Using the same "generic" and "specific" health assessment tools it then evaluates the health status of a comparable group of men 4 weeks prior and 24 months after, a hip fracture.

The populations studied (hip fracture cases and community controls) are those detailed in chapter 2. The Short Form-36 (SF-36) was used as the "generic" health assessment questionnaire and a modification of the (Health Assessment Questionnaires) HAQ termed "HAS" was used for assessing functional ability. A single interviewer administered the questionnaires within 48 hours of the fracture in cases and at the time of the first visit in the controls. They were re-administered at 6, 12 and 24 months.

In all 8 domains of the SF-36, quality of life amongst community controls was comparable to standard US norms. The physical component score (PCS) was 0.5SD below and the mental component score (MCS) 0.7SD above the published US scores. Cases scored poorly in all domains of the SF-36 except pain compared to controls both before and upto 24 months after the hip fracture ($p<0.001$). The magnitude of difference observed between the two groups using the PCS, MCS and after adjustment for the confounding effects of age and co-morbidity remained unchanged. Fracture resulted in reduction of the PCS from 40.5 at baseline to 35.6, 35.4 and 33.3 at 6, 12 and 24 months respectively. After adjusting for group differences in age, co-morbidity and baseline physical function, presence of fracture reduced PCS by approximately 0.5SD at each assessment interval. The effect on the MCS was less dramatic.

A good correlation was seen between the PCS and the health assessment score (HAS); $r=-0.76$, $p<0.001$. Cases scored higher (worse) compared to controls, at first visit (0.83 Vs 0.27, $p<0.001$). Similar differences were observed at 6, 12 and 24 months. Hip fracture had an immediate and pronounced effect on the HAS with an increase (worsening) of the score from 0.83 at baseline to 1.2 at 6 months.

Overall the health status of our control population was comparable to the standards laid out for the US general population. Poor general health is a characteristic feature of men who sustain a low trauma hip fracture, and is evident at least 4 weeks prior to the episode. Hip

fracture results in an immediate decline in physical function, which continues to deteriorate steadily over 2 years; the effect on mental functions is less marked. After adjusting for differences in age, co-morbidities and "pre-fracture" functional dependence between the two populations at baseline, this study shows that fracture status independently influences an individuals quality of life for upto 2 years.

10.2 BACKGROUND

Over recent years there has been an explosion in the utilisation of health related quality of life instruments for a wide variety of diseases. Various generic instruments to measure quality of life have been developed with one, the Short Form-36 (SF-36), being widely adopted by many researchers. The SF-36 has been well validated for use in many countries and for many diseases.

Disease specific instruments have been developed with the aim of evaluating specific quality of life issues relevant to patients with a particular disease. In the absence of any well accepted "specific" quality of life instrument for osteoporotic hip fracture patients the questionnaire used by the Mediterranean osteoporosis study (MEDOS) was considered suitable as a prototype. To simplify analysis and interpretation it was scored similar to the health assessment questionnaire (HAQ) used in rheumatoid arthritis. The validity and responsiveness of this questionnaire over time has yet to be established.

There have been several studies addressing impact of osteoporotic fractures on quality of life and function of individual subjects. Most of these studies are focused at women. In addition, few have directly compared with age matched normal subjects without fracture. There are also no studies looking at both pre and post fracture health status.

An evaluation of the specific impact of hip fracture on quality of life and function is important in determining the nature and magnitude of the health deficits associated with hip fracture.

This section compares the quality of life and function in 100 men with hip fracture to 100 comparable controls living in community who have not had a hip fracture. Due to the inherent properties of the SF-36 questionnaire, baseline assessment is the best possible estimate of the "pre-fracture" quality of life of the individual using such a study design. The modified MEDOS questionnaire termed the health assessment score "HAS" allowed assessment of many of the simpler tasks of daily life including eating, grooming and toileting

(Appendix 2.3). The combination of these tools with prospective assessment over 24 months gave the best possible estimate of health related quality of life following a hip fracture in elderly men.

10.3 MATERIAL AND METHODS

10.3.1 Recruitment of subjects

The study used a case control design with simultaneous and prospective recruitment of hip fracture cases and community controls over 14 months. Details of inclusion and exclusion criteria and study design are described in chapter 2.

10.3.2 Assessment of quality of life using generic SF-36

The SF-36 (see Appendix 2.3) was administered in the standardised manner, with no interpretation of the questions by the interviewer. This instrument measures quality of life in eight domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), role emotional (RE) and mental health (MH) (for a definition of terms see Table 1 under Appendices). From these eight domains two summary scores were calculated: these were the physical and mental component summary indexes (PCS and MCS) respectively (see Figure 1 under Appendices).

The SF-36 was administered to all controls at the time of the first visit and to cases within 48 hours of the hip fracture. Baseline questionnaire assessed quality of life 4 weeks prior to the event. The SF-36 questionnaire was re-administered amongst consenting survivors in both groups at 6, 12 and 24 months. Where subjects were incapable of completing the questionnaire proxy members were not considered appropriate. These subjects were excluded from the analysis. Missing observations were largely due to death and dementia. Since the questionnaire was administered in the hospital setting, the form was checked for its completeness before the subject completed his visit. As a result problems in handling missing data were avoided.

10.3.3 Assessment of functional capacity using HAS

Functional capacity related to activities of daily living was assessed using another questionnaire (see Appendix 2.3) that was co-administered with the SF-36 in both cases and controls. This questionnaire was based on one used by the MEDOS (Mediterranean Osteoporosis Study) group and assessed degree of functional limitation in eight activities:

ability to dress/ undress, ability to eat, perform household chores, get up from a chair, climb stairs, wash and dry, walk indoors and outdoors. The response was graded: without difficulty = 0; with some difficulty =1, with much difficulty = 2 and unable to do = 3. Use of an aid/ device or help from another person in performing any activity was scored as 2.

Similar to the Health Assessment Questionnaire (HAQ) used in rheumatoid arthritis subjects the sum of all the eight individual scores gave a score ranging between 0 (independent) to 24 (totally dependent). All the eight activities were equally weighted as in HAQ and the total score was then divided by 8 to give a composite health assessment score (HAS) ranging between 0-3 where 0 equals the best score and 3 the worst.

Similar, to the SF-36 the HAS was evaluated at baseline, 6, 12 and 24 months in both cases and controls. Missing observations were due to death and dementia.

10.3.4 Assessment of co-morbidity

Interviewer assisted questionnaire (see Appendix 2.2) also captured details of co-morbidity and concomitant medication from the information supplied by the subject and review of medical records. The co-morbidity score for each subject was calculated by adding the number of co-morbid diseases. List of medications specially those likely to affect bone metabolism namely calcium, corticosteroids, antiepileptics, bisphosphonates, vitamin D were noted.

10.4 STATISTICAL ANALYSIS

All data was entered in EXCEL and then transferred for analysis to SPSS and STATA. Descriptive statistics were used to characterise the study subjects. In addition to deriving original scores for all the 8 domains of the SF-36, two quality of life summary statistics- the physical and mental component summary scores (PCS and MCS)- were calculated from the physical and mental health domains of the SF-36 using previously established methods. The correlation coefficient estimates were made using Spearman Rho. Independent sample t test were used to compare SF-36 and HAS between groups and paired t test was used to assess longitudinal change within groups over the 24 month follow-up. The PCS and MCS scores of our study cohort were also compared to the standardised scores published for the US general population. Linear regression was used to analyse the independent effects of fracture status on PCS and MCS during different stages of the study period.

10.5 RESULTS

Fracture cases were older and had significantly more co-morbidities than the control population (Table10.1). A greater proportion of cases consumed antipsychotics, antiepileptics and diuretics. The number of controls reporting intake of over the counter "health tablets" like multivitamins, calcium, vitamin D, cod liver oil etc. were significantly higher than cases (17% Vs 1%, $=\chi^2=14.9$, df=1, $p<0.001$).

Within group correlation analysis of both fracture and control subjects showed the SF-36 physical component score was related to the HAS. r_s=-0.76; $p<0.0001$, n=81 for cases and r_s =-0.71, $p<0.0001$, n=99 for controls.

Table 10.1 Descriptive characteristics of cases and controls

	Cases (%)	Controls (%)	Significance
Mean age (years)	79.9	75.1	<0.01
Cerebrovascular diseases	25.4	8.4	χ^2=9.4, df=1, p<0.001
Parkinson's	14.6	1.1	χ^2=12.1, df=1, p<0.001
Dementia	27.1	2.1	χ^2=23.5, df=1, p<0.0001
Reduced mobility	26.0	4.2	χ^2=17.6, df=1, p<0.0001
Poor vision	21.9	7.4	χ^2=8.0, df=1, p<0.005
Antipsychotics	8.3	0	χ^2=18.3, df=1, p<0.004
Antiepileptics	6.3	0	χ^2=6.1, df=1, p<0.01
Diuretics	30.2	15.8	χ^2=5.6, df=1, p<0.02
Presence of co-morbidity	79.9	64.1	χ^2=5.5, df=1, p<0.02

10.5.1 Quality of life assessed using SF-36 in controls

The SF 36 questionnaire was completed by all controls at baseline but only 97, 87 and 84 men at 6, 12 and 24 months respectively. The mean scores in the 8 domains at first visit are shown in fig 10.1b. The results are comparable to the means standardised for the general US population fig 10.1a.

The summary indices i.e. physical and mental component scores (PCS & MCS) are shown in figures 10.2. Both scores showed a decline, although the change in physical score (-0.5SD) was greater than the reduction in the mental score (-0.3SD) over the 24 month follow-up period. The physical scores were 0.5SD below the mean US standard at baseline and

deteriorated to 0.9SD below the US mean by 2 years. In contrast, controls consistently scored higher on the mental scores compared to the US standards. They scored +0.6SD higher at first visit and remained high by +0.4SD above the US mean at 2 years.

Figure 10.3 illustrates the paired changes in PCS and MCS between baseline- 6 months, baseline-1 year and baseline-2 years. The observed decline in scores at all time points was significant (paired t test $p<0.05$ for all pairs 0-6, 0-12 and 0-24 months).

10.5.2 Functional capacity using Health Assessment Score (HAS) in controls

Questionnaire used to calculate the health assessment score (HAS) was completed by 99, 97, 87 and 84 controls at baseline, 6, 12 and 24 months respectively. The score ranged from 0 to 3 with zero representing the best score implying functional independence. The mean HAS at first visit was 0.27. The score increased to 0.40 at 6 months and then remained at 0.36 and 0.39 at 1 and 2 years respectively (fig 10.4). HAS showed an increase (worsening) in 31 of the 96 controls reassessed at 6 months compared to baseline (Wilcoxon signed ranks test $p<0.001$). Further change in the score was observed at 12 and 24 months with 34 of the 86 and 30 of the 83 exhibiting a further increase (Wilcoxon signed ranks test $p<0.001$).

Detailed analysis of the 8 activities assessed (ability to eat, dress, perform household chores, get up from a chair, do stairs, wash and dry, walk indoors and outdoors) at the four time scales (baseline, 6, 12 and 24 months) is attached in appendix 3. At first visit 87% could walk unaided, 77% get up from a chair without difficulty and 64% climb stairs. Only 1 subject was unable to walk. At 1 year these figures had changed to 84%, 59% and 67% and by 2 years they were 85%, 62% and 56% respectively.

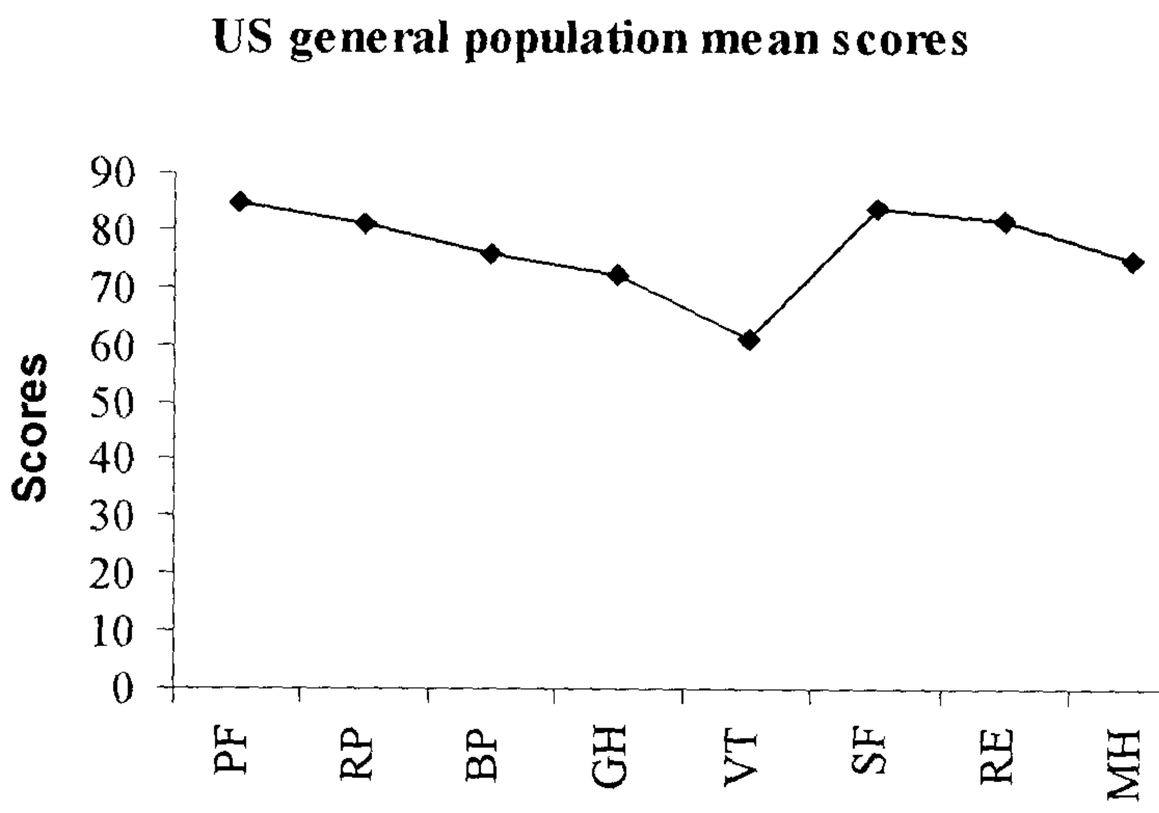


Figure 10.1a Mean SF-36 scores of the standard US general population
PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

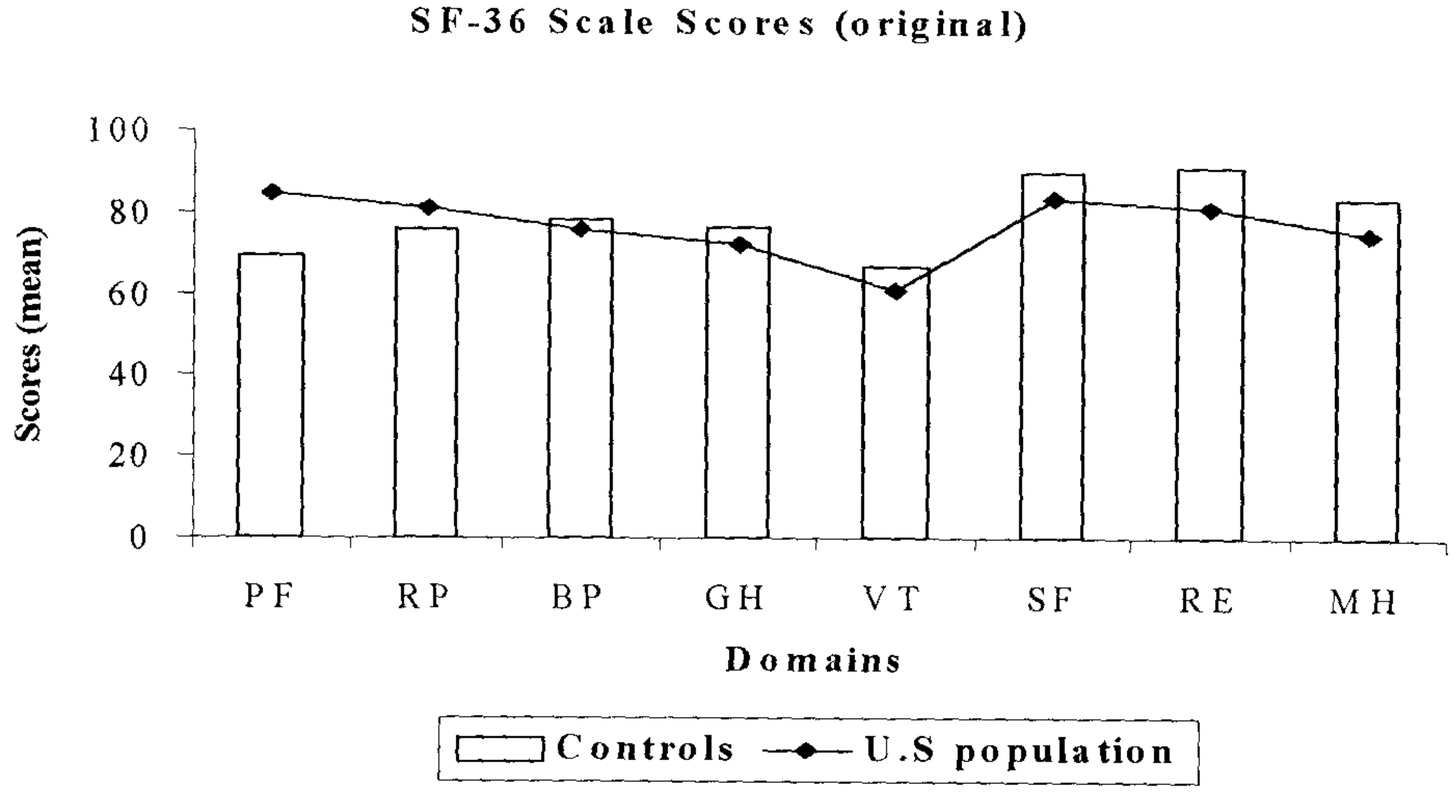


Figure 10.1b SF-36 scores at baseline in controls standardised to US general population
PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

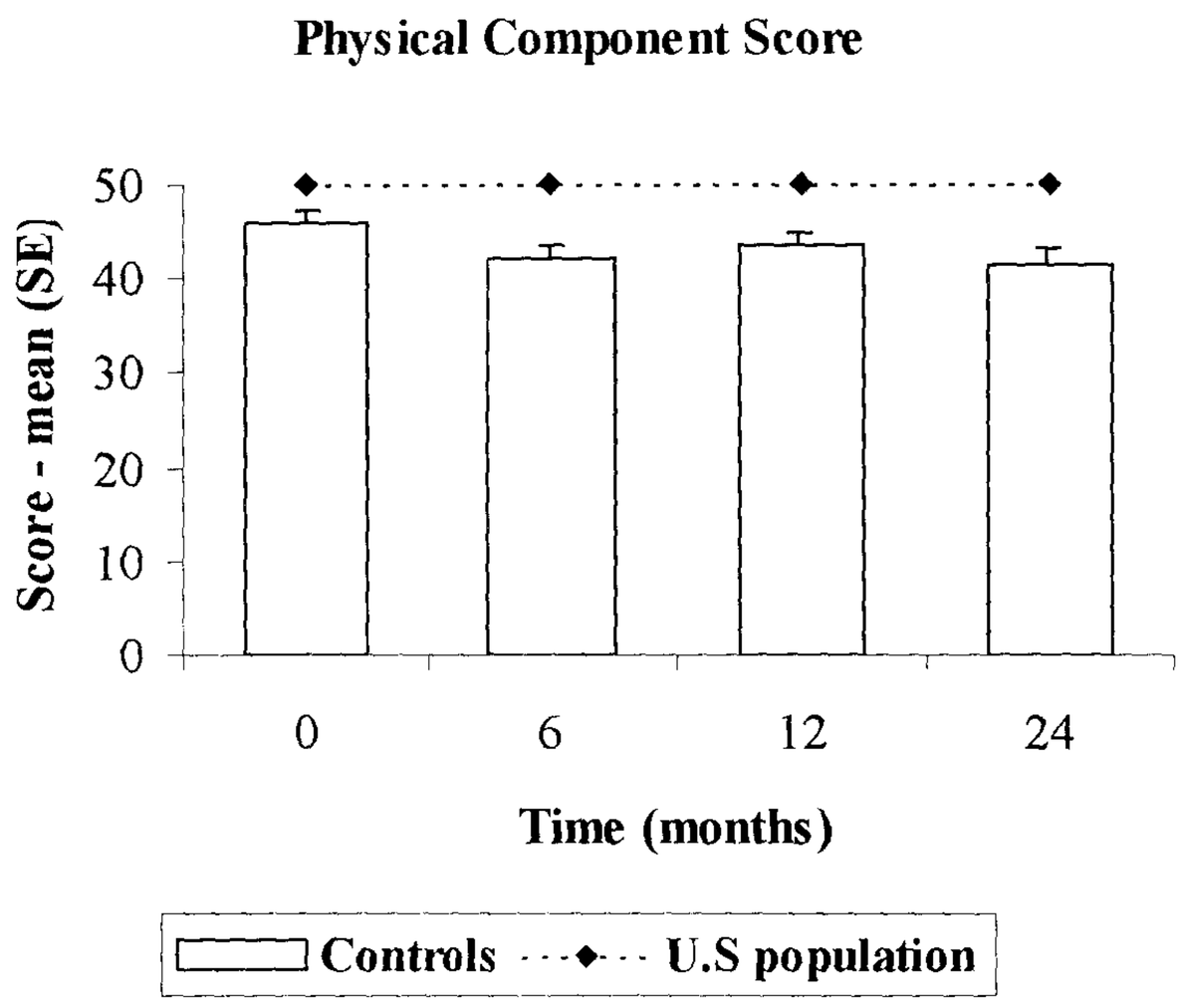


Figure 10.2a Physical component score (PCS) in controls over 2 years
Mean (SD) PCS for the US population: 50 (10)

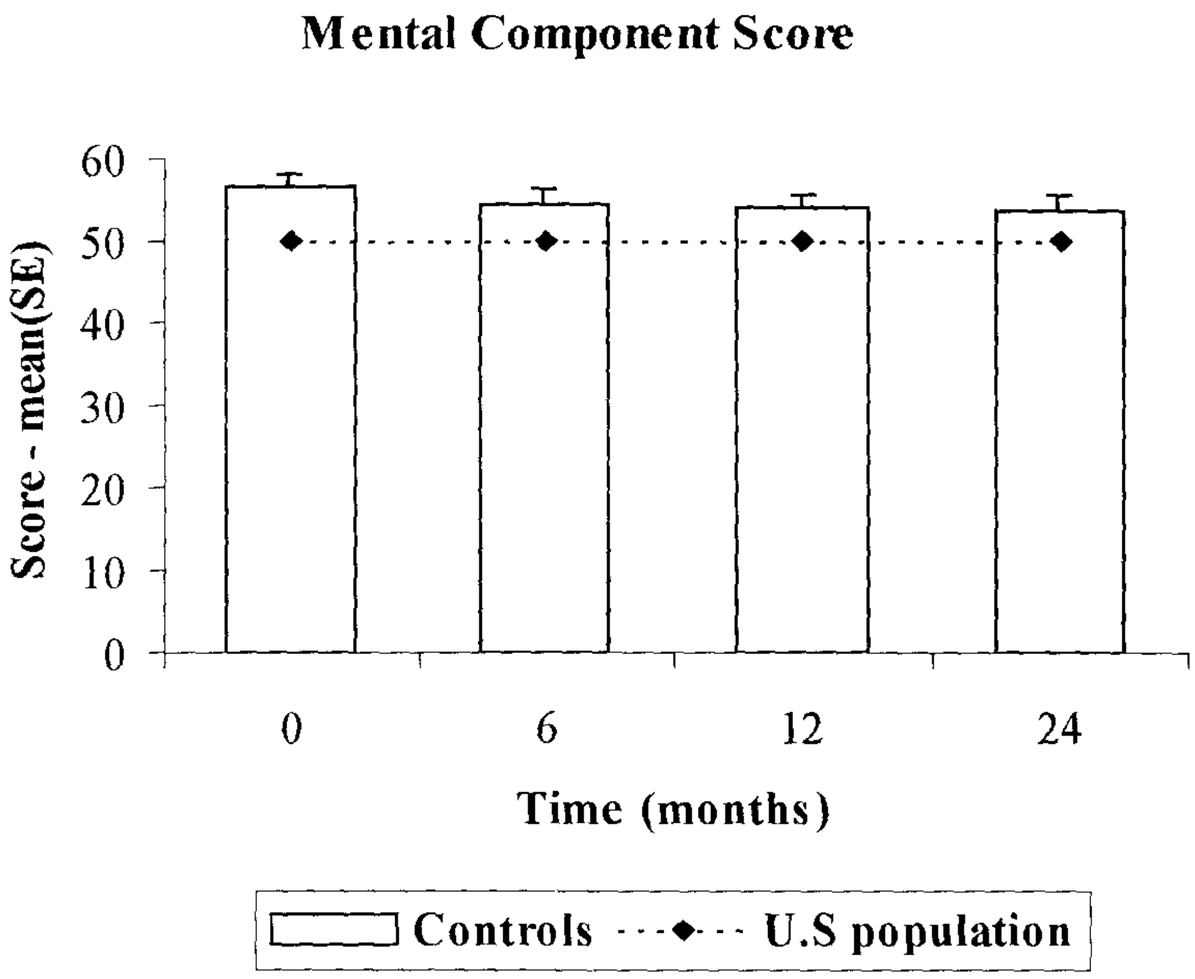


Figure 10.2b: Mental component score (MCS) in controls over 2 years
Mean (SD) MCS for the US population: 50 (10)

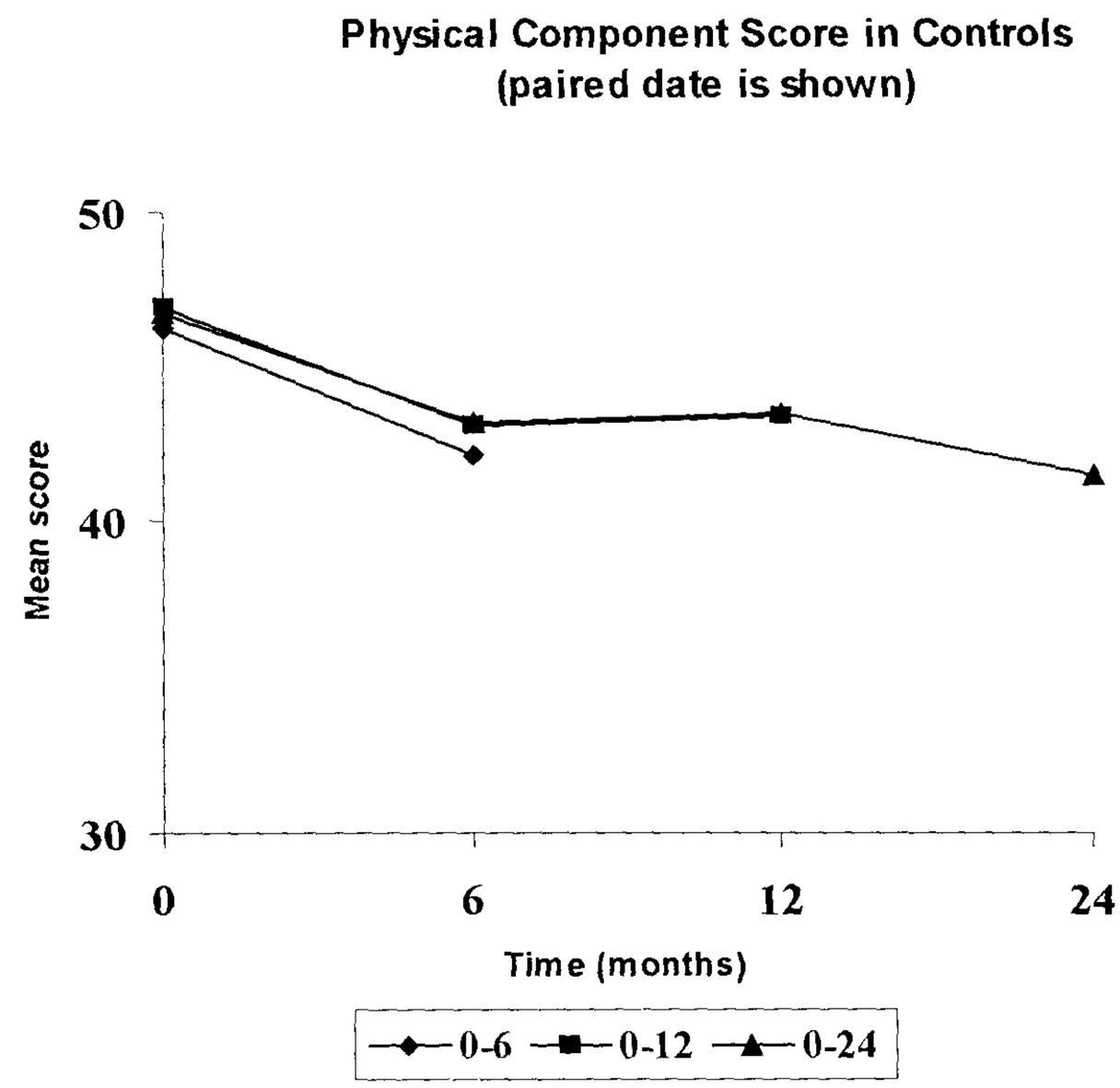


Figure 10.3a: Changes in Physical component score in Controls over 2 years
Paired data are shown as individual lines

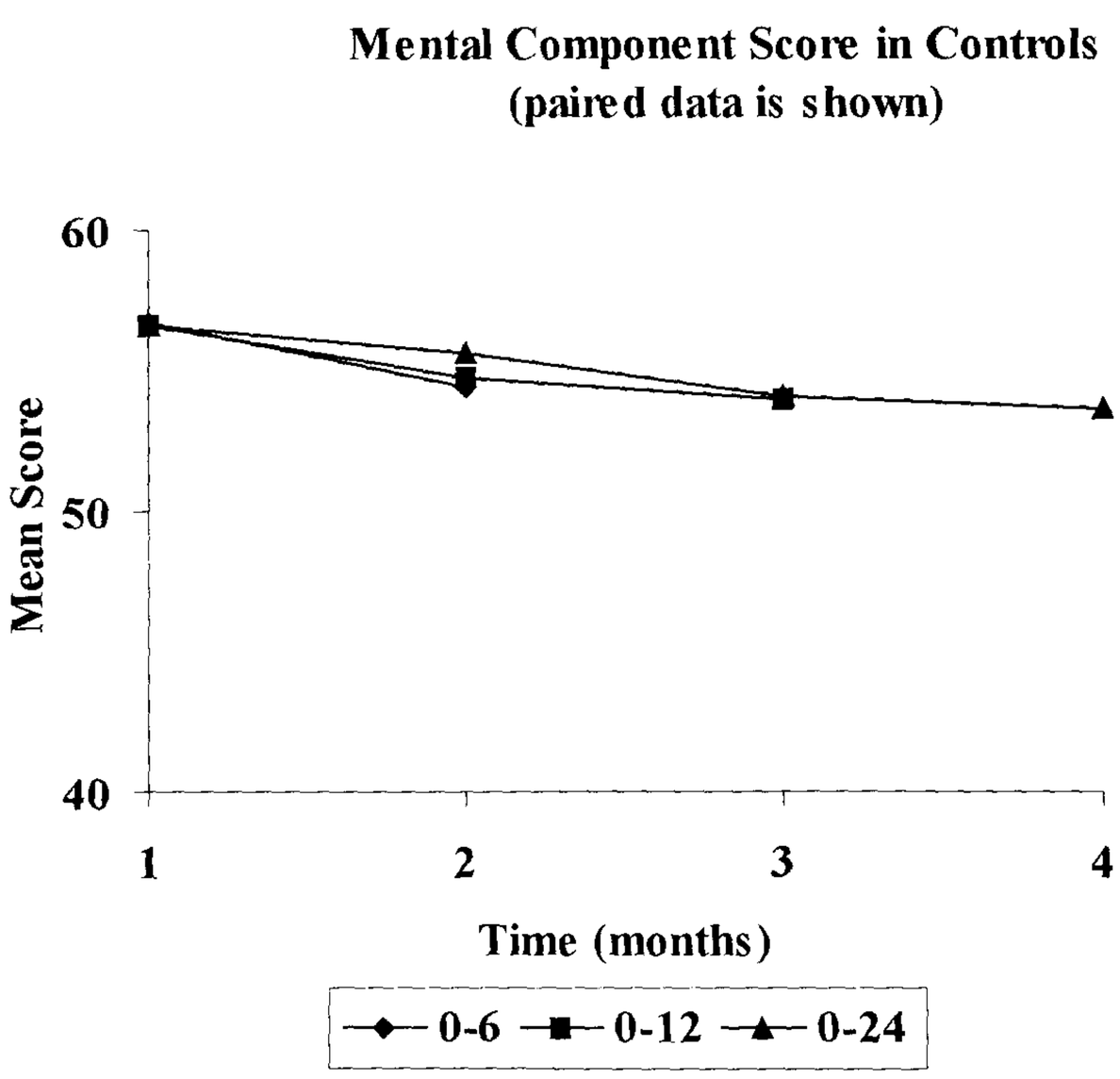


Figure 10.3b: Changes in Mental component score in Controls over 2 years

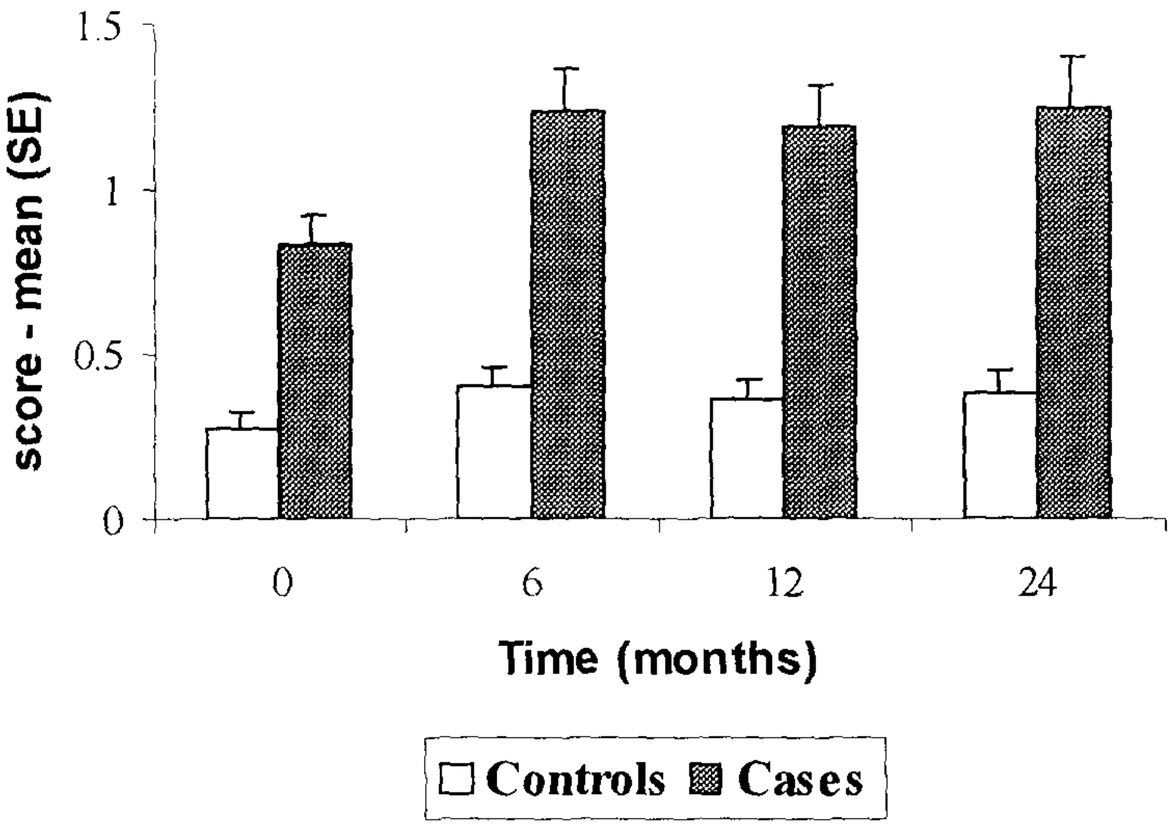


Figure 10.4: Health Assessment Score (HAS) in cases and controls over 2 years

10.5.3 Quality of life in hip fracture cases

Only 81 cases completed the SF 36 questionnaire within 48 hours of the hip fracture. Follow-up scores at 6, 12 and 24 months were available in 51, 47 and 34 cases respectively. Baseline SF-36 scores reflected the "pre-fracture" health status. The pre-fracture mean scores in the 8 domains and their comparison with the controls are shown in figure 10.5. Cases scored significantly worse in all domains except pain (BP). The results of the composite physical and mental component scores are shown in figure 10.6. Even before the fracture cases scored significantly lower in both the PCS and MCS compared to controls. Pre-fracture mean physical score in the cases was more than 1 SD below the standard US mean. Pre-fracture mental scores although significantly less than the controls were normal by US standards. The immediate effect of fracture was seen on the physical but not on the mental component summary index see fig 10.5. Following the fracture the physical scores deteriorated steadily to more than 1.7 SD below the US mean at 2 years. The fracture event did not have an immediate effect on the mental scores (p=NS at 1 year). However, a significant later decline in MCS was observed at 2 years ($p<0.04$).

Figure 10.7a illustrates the paired changes in PCS between baseline- 6 months, baseline -1 year and baseline-2 years. The decline in PCS was significant (paired t test $p<0.05$ for all pairs 0-6, 0-12 and 0-24 months). The change in MCS (fig 10.7b) was significant only between baseline and 2 years (mean 50.1 at baseline, 45.1 at 2 years; paired t test $p<0.035$).

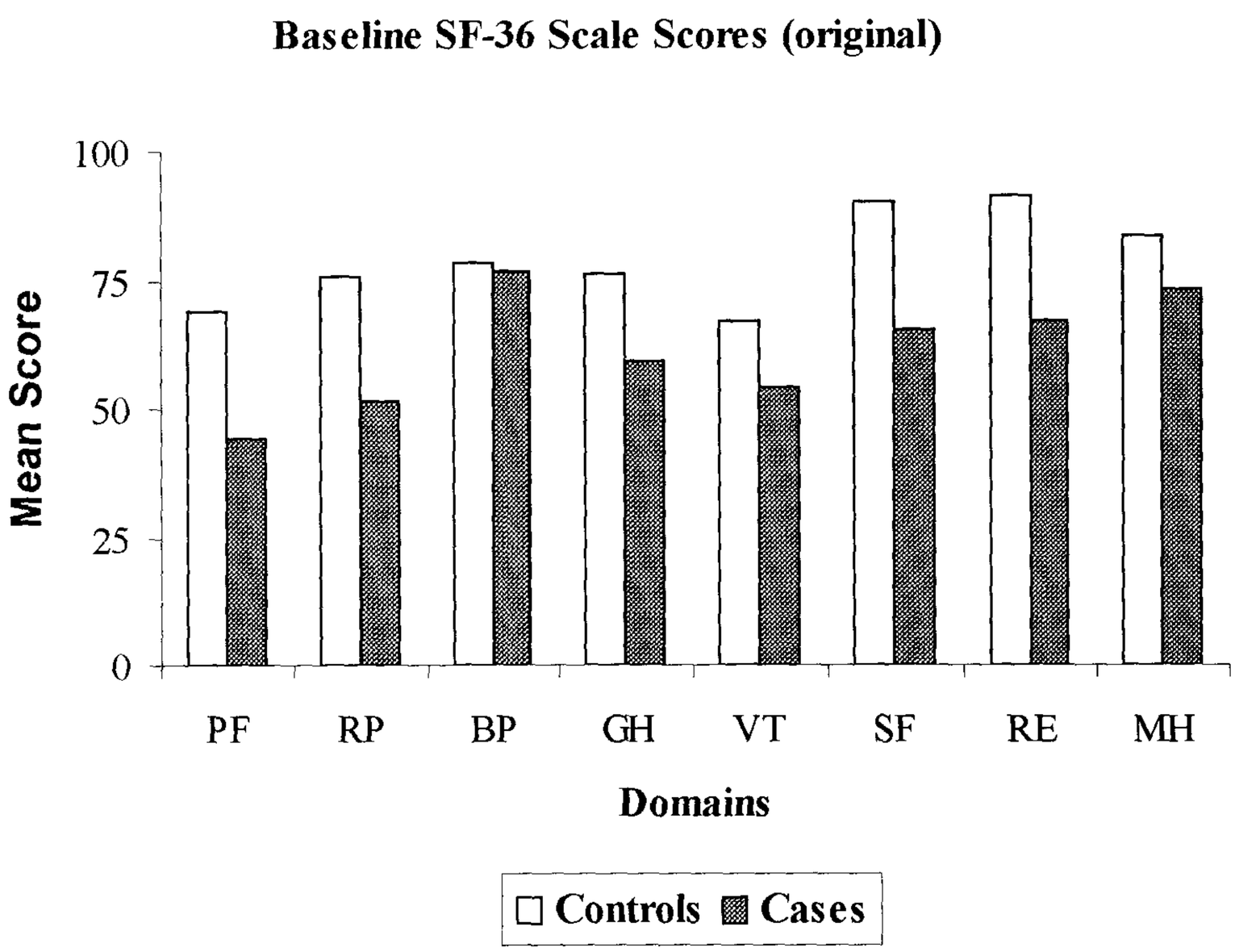


Figure 10.5: Mean SF-36 scores at baseline in cases and controls

PF: physical functioning, RP: role-physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role-emotional, MH: mental health

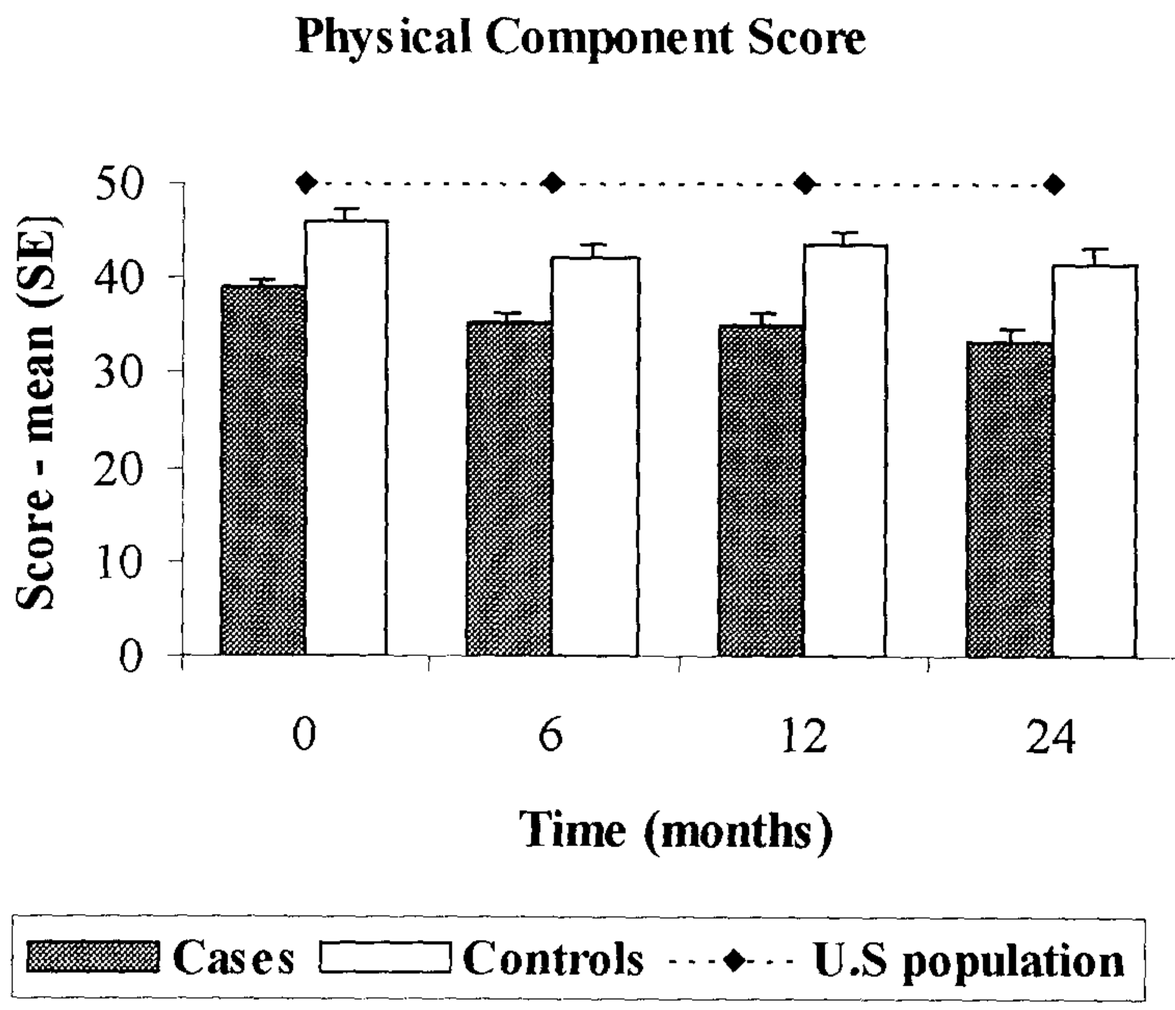


Figure 10.6a: Physical component score (PCS) in cases and controls over 2 years
Mean (SD) PCS for the US population: 50 (10)

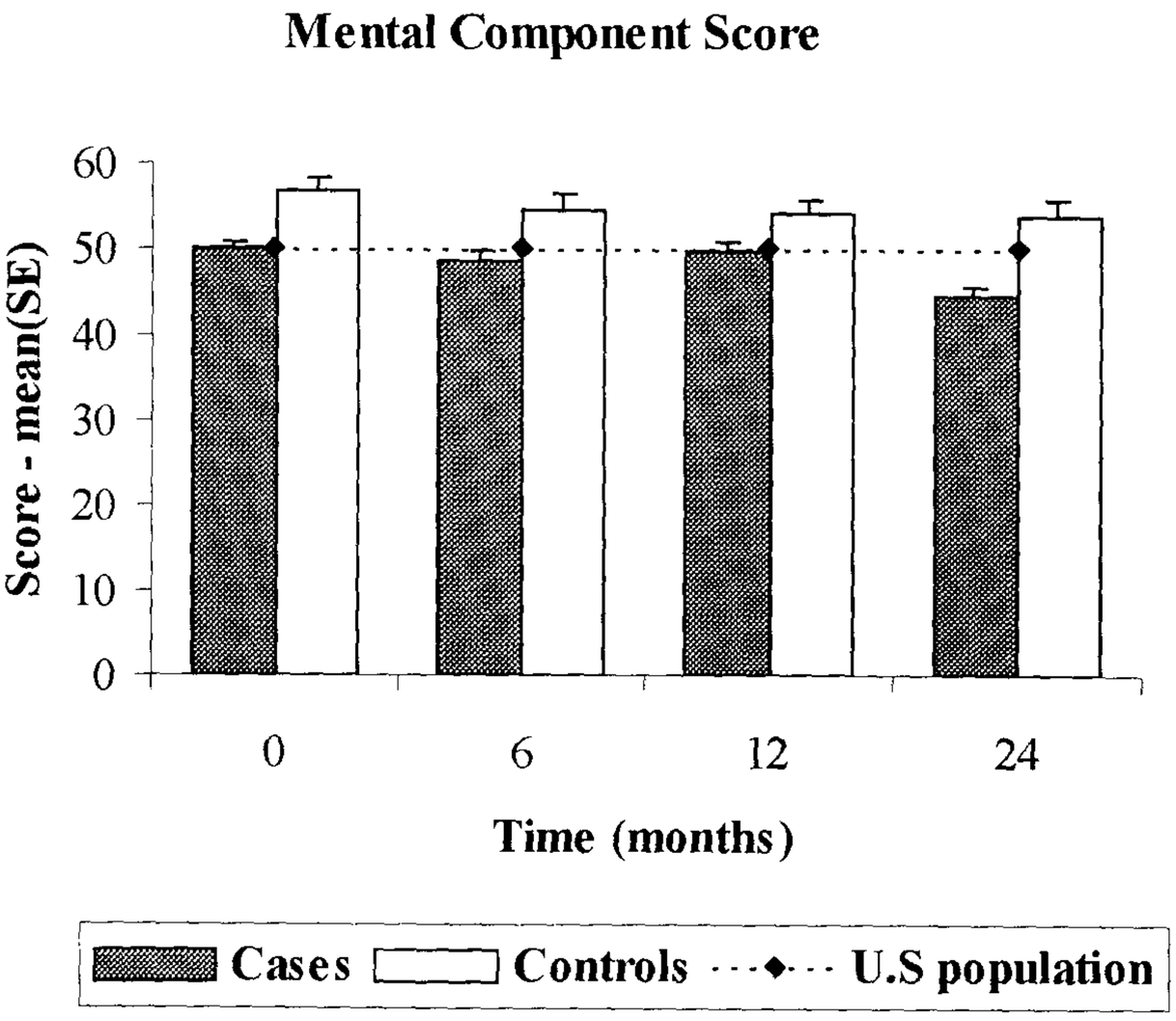


Figure 10.6b: Mental component score (MCS) in cases and controls over 2 years
Mean (SD) MCS for the US population: 50 (10)

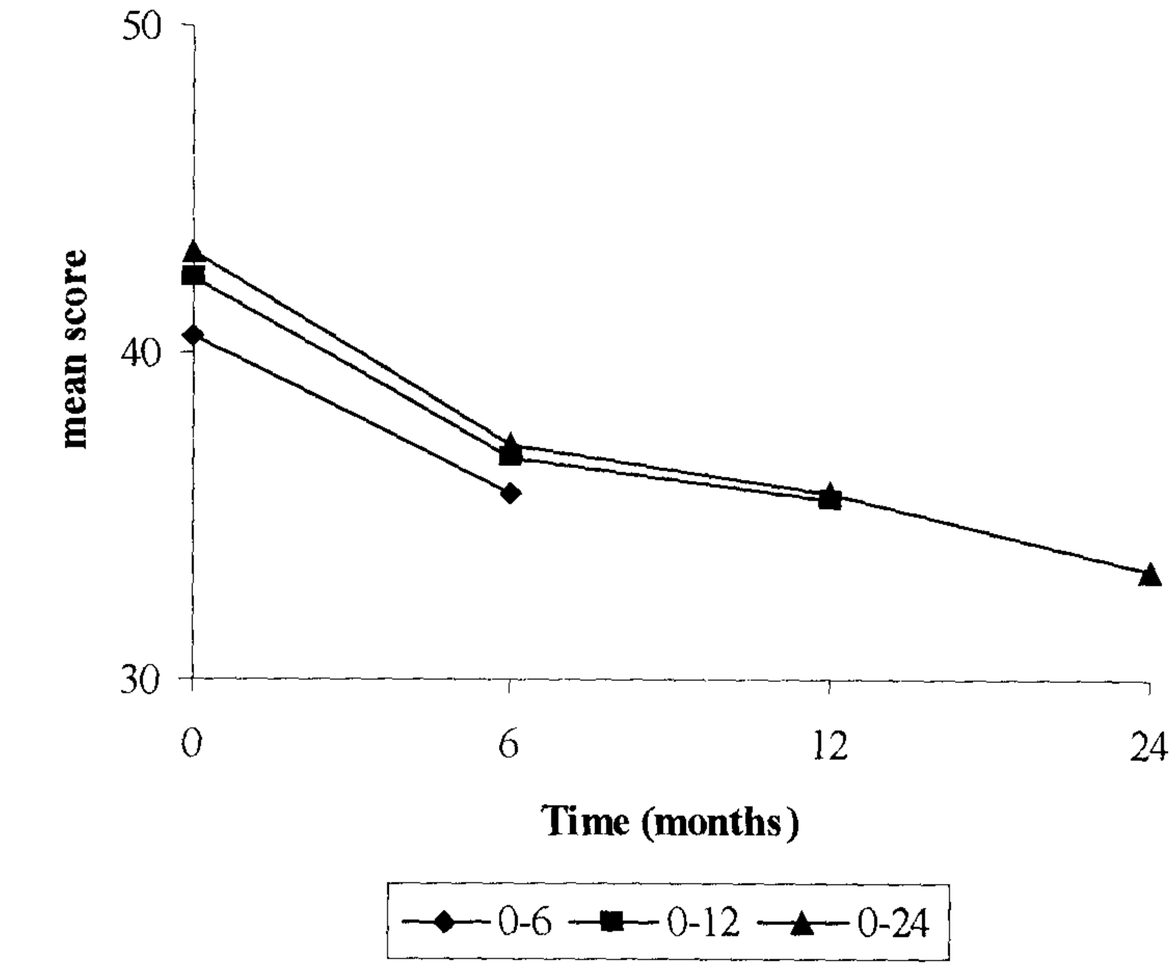


Figure 10.7a: Changes in Physical component score in Cases over 2 years
Paired data are shown as individual lines

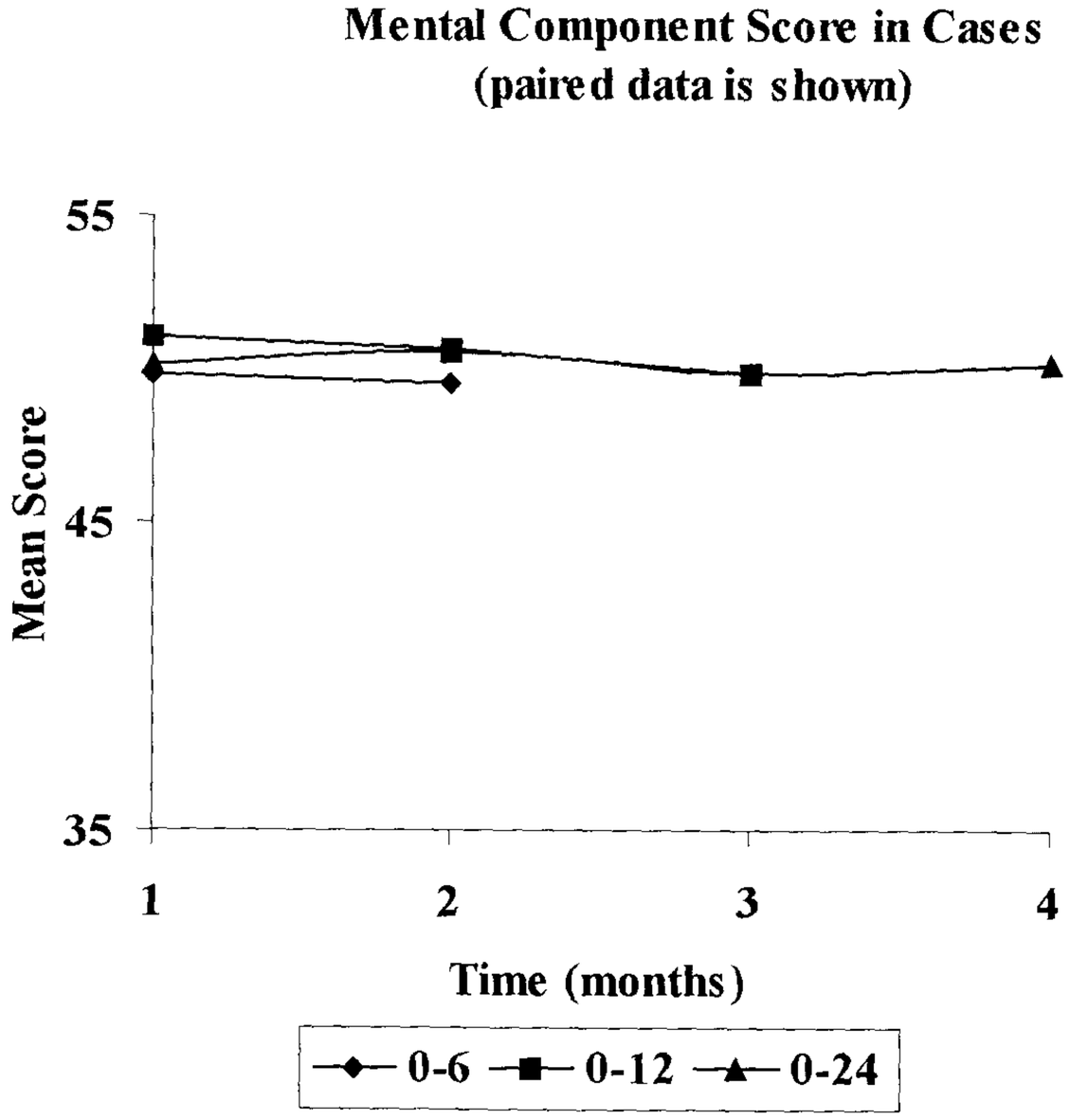


Figure 10.7b: Changes in Mental component score in Cases over 2 years

10.5.4 Functional capacity in cases

Questionnaire used to calculate the health assessment score were completed by 91, 50, 47 and 35 cases at baseline, 6, 12 and 24 months respectively The mean HAS at baseline was 0.84. Fracture raised the HAS of the 50 survivors at 6 months to 1.2. The score stabilised at 1.2 amongst survivors reassessed at 12 and 24 months (fig 10.4).

Paired t test was used to analyse change in the score between two time points i.e. baseline-6 months, baseline-12 months and baseline-24 months. 31 of the 47 cases assessed both at baseline and 6 months, 34 of the 45 assessed at baseline and at 12 months and 27 of the 34 assessed at baseline and at 24 months scored higher than their initial values; paired t test $p<0.001$.

Detailed analysis of the 8 activities assessed in the HAS at the four time scales (baseline, 6, 12 and 24 months) is attached in appendix 3. Before fracture 59% could walk unaided, 51% could get up from a chair without difficulty and 40% could climb stairs without difficulty. Only 4% subjects were unable to walk. At 1 year these figures had changed to 36%, 37% and 15% and by 2 years they were 34%, 26% and 20% respectively. A significant proportion (15% & 20% respectively) were unable to walk at 12 and 24 months post fracture.

10.5.5 Quality of life in cases compared to controls

Fracture cases had worse scores in all domains except pain compared to controls both before and upto 24 months after the hip fracture. This was also true using the physical and mental component score. These differences in SF-36 physical and mental component scores persisted even when baseline differences in age and co-morbidities were allowed for in the multiple regression analysis (Table 10.2). This indicates that fracture status was a significant and independent determinant of quality of life.

Table 10.2 Determinants of the SF-36 physical component score at 6 months as the dependent variable

Model	Unstandardized Coefficients		Standardized coefficients	Significance level
	B	Standard Error	Beta	
Constant	65.29	7.03		0.001
Age	-0.24	0.09	-0.19	0.01
Co-morbidities	-8.02	1.96	-0.31	0.001
Fracture status	-5.30	1.85	-0.21	0.001

Regression analysis was undertaken entering the independent variables age, presence of co-morbidities and fracture status into the analysis. The overall correlation coefficient was $r=0.48$, $p<0.0001$.

Determinants of the SF-36 physical component score at 12 months as the dependent variable

Model	Unstandardized Coefficients		Standardized coefficients	Significance level
	B	Standard Error	Beta	
Constant	30.03	7.52		0.001
Age	-0.17	0.08	-0.14	0.04
Co-morbidities	-3.27	1.78	-0.13	0.07
PCS (baseline)	0.60	0.08	0.51	0.001
Fracture status	-4.50	1.71	-0.18	0.01

Regression analysis was undertaken entering the independent variables age, presence of co-morbidities, physical component scores at first visit and fracture status into the analysis. The overall correlation coefficient was $r=0.67$, $p<0.0001$.

Determinants of the SF-36 physical component score at 12 months as the dependent variable

Model	Unstandardized Coefficients		Standardized coefficients	Significance level
	B	Standard Error	Beta	
Constant	57.43	6.75		0.001
Age	-0.13	0.09	-0.10	0.17
Co-morbidities	-4.35	1.88	-0.17	0.02
HAS (baseline)	-8.14	1.50	-0.42	0.001
Fracture status	-4.96	1.79	-0.42	0.001

Regression analysis was undertaken entering the independent variables age, presence of co-morbidities, health assessment scores at first visit and fracture status into the analysis. The overall correlation coefficient was $r=0.61$, $p<0.0001$.

Determinants of the SF-36 physical component score at 24 months as the dependent variable

Model	Unstandardized Coefficients		Standardized coefficients	Significance level
	B	Standard Error	Beta	
Constant	47.11	8.06		0.001
Age	-0.37	0.09	-0.29	0.00
Co-morbidities	-4.04	1.81	-0.16	0.03
PCS (baseline)	0.52	0.09	0.45	0.001
Fracture status	-6.27	1.84	-0.24	0.00

Regression analysis was undertaken entering the independent variables age, presence of co-morbidities, physical component scores at first visit and fracture status into the analysis. The overall correlation coefficient was $r=0.69$, $p<0.0001$.

Determinants of the SF-36 *mental* component score at 6 months as the dependent variable

Model	Unstandardized Coefficients		Standardized coefficients	Significance level
	B	Standard Error	Beta	
Constant	58.53	7.16		0.001
Age	-0.04	0.10	-0.03	0.68
Co-morbidities	-1.68	2.00	-0.07	0.40
PCS (baseline)				
Fracture status	-5.49	1.88	-0.24	0.001

Regression analysis was undertaken entering the independent variables age, presence of co-morbidities, visit and fracture status into the analysis. The overall correlation coefficient was $r=0.27$, $p<0.01$

10.5.6 Functional capacity in cases compared to controls

Cases consistently scored higher (worse) than controls at all time points ($p<0.001$) see figure 10.8. The rate of change in the HAS was significantly greater in cases compared to controls between any two assessment points. The change in the scores over time period varied between -0.12 and -0.17 in the controls compared to -0.49 and -0.63 in cases (figure 10.8)

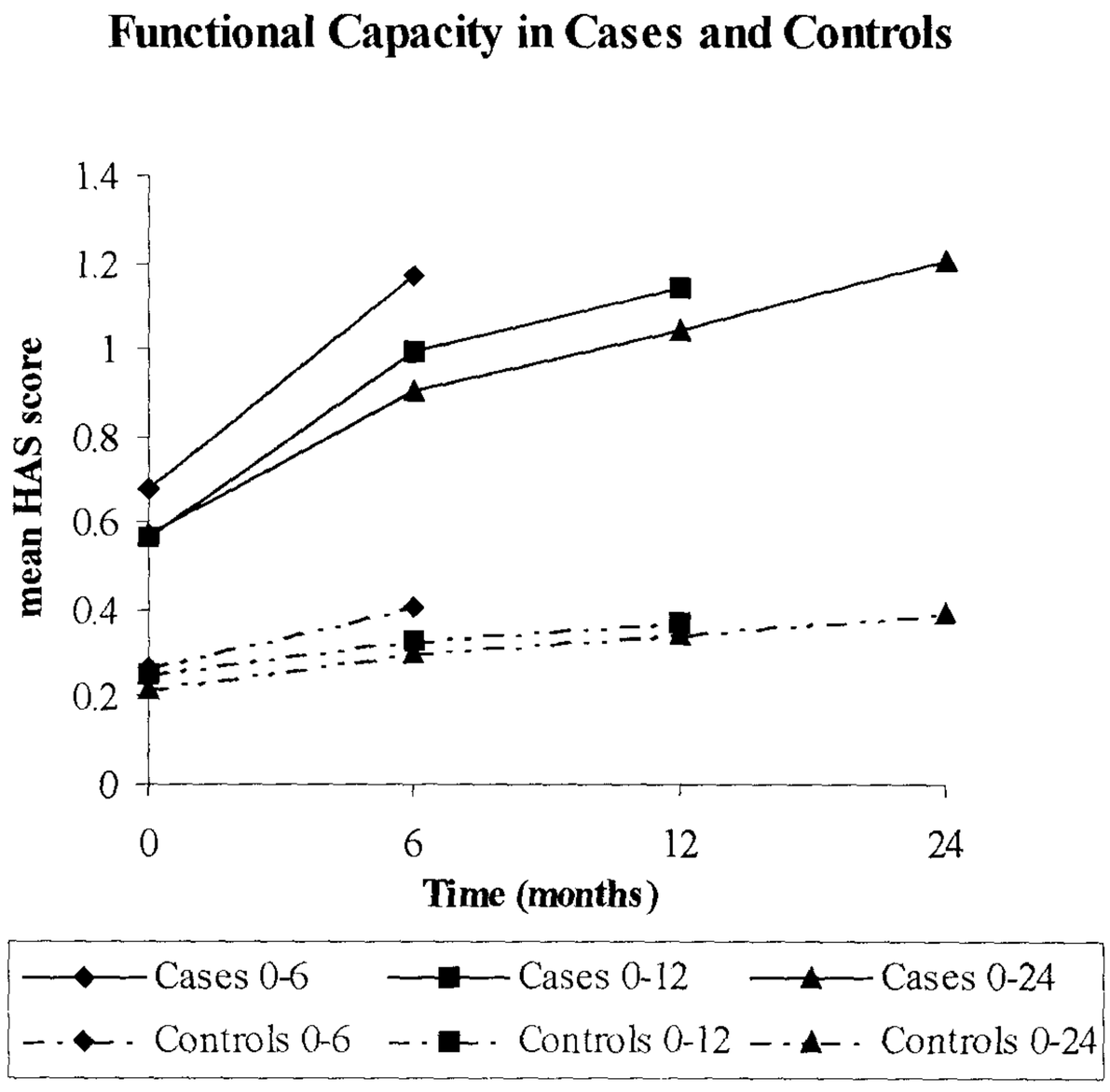


Figure 10.8: Health Assessment Score in cases and controls over 2 years

10.5.7 Fracture status as a determinant of quality of life

There were significant differences in age, number of co-morbidities and baseline physical functional status between the two study groups. To assess the independent effect of hip fracture on "quality of life" linear regression was used with the dependent variable as the physical or mental component score at a time point and independent variable age, presence of co-morbidities, baseline PCS or HAS and fracture status. At each assessment (6, 12 and 24 months) occurrence of hip fracture was associated with a significant reduction in the physical scores see Table 2. Presence of hip fracture decreased the PCS at any assessment interval by approximately -5.0 (-5.3, -4.5, -6.3 at 6, 12 and 24 months respectively). This is equal to 0.5SD reduction by published US norms. The effects on mental functions were less

obvious. This indicates that fracture status was a significant determinant in the reduction of quality of life in the fracture subjects, which was not fully accounted for by poor physical and health assessment scores. Furthermore it was not primarily due to group differences in age, co-morbidity, PCS and HAS scores.

10.6 CONCLUSIONS

Controls, chosen at random from the same community population as the fracture subjects, are a good representative of the "general population" as their quality of life is comparable to published standards. Poor health status is characteristic of men who present with a low trauma hip fracture and is measurable/ quantifiable 4 weeks prior to the episode. Two of the SF-36 domains, physical health and mental health, illustrate the magnitude of the reduction in quality of life measures between the hip fracture and controls group. Poorer health status remains the hallmark of this population even 2 years after the fracture. Hip fracture has a detrimental effect on physical function, which is immediate and exhibits a continuos decline upto 2 years. The effect on mental function is less marked and only reached significance at 2-years.

The health assessment score (HAS) developed for this study is a good measure of the subjects' physical function. It correlated with the physical component score derived from the SF-36. The within group correlation analysis was r_s =-0.76; p<0.0001, n=81 for cases and r_s =-0.71, p<0.0001, n=99 for controls. Similar to the results obtained using the SF-36, the HAS was significantly higher (worse) in cases compared to control and remained so till 2 years after fracture.

SF-36 scores and HAS were not available in a significant number of subjects in both groups. Missing observations in the majority were due to mortality, dementia, frailty and refusal. It is likely that these individuals were less healthy and more debilitated. If true, the effect of this would be to underestimate the poor health associated with hip fracture and the strength of the association between fracture and quality of life.

In the absence of a population based longitudinal study SF36 scores obtained within 48 hours of admission are the best pre-fracture estimates for the individual. However, bias towards documenting poor health as a result of hospitalisation cannot be completely ruled out. Finding no differences in the pain score between the two groups at baseline despite a recent fracture gives reason to believe that this was not the case.

Group differences in age, number of co-morbidities, baseline dependency level as measured using both PCS and HAS may be responsible for the poor quality of life in fracture cases compared to controls over the 2 year follow-up. However, even when these differences were allowed for, the presence of hip fracture still had a significant effect on both the physical and mental spheres of quality of life until 2 years. This suggests that hip fracture had global and severe effects on the affected individual until 2 years that were only partly dependent on their reduction in functionality prior to fracture.

11. MORTALITY AND PROGNOSTIC FACTORS

11.1 SUMMARY

This chapter addresses the mortality and causes thereof, associated with low trauma hip fracture in men. A comparison is made to a control population. Factors that influence the mortality associated with fracture are examined.

The study population is the same as outlined in chapter 2. 100 men with hip fracture and 100 controls from the community were followed for a mean of 661 days (1.8 years) range 2-1128 days. The follow-up was 100% in both groups. Mortality was 60% in the hip fracture population against 10% amongst controls. After adjusting for age differences between the two study populations, presence of hip fracture increased the risk of death 8 fold (HR=8.1 95%CI 4.1, 16.0). Causes of death were similar in the two groups: chest infections and heart disease being the commonest.

Age was the single dominant factor influencing death (HR=1.1 for each year increase in age) following hip fracture. Men over 70 were more likely to die (HR=5.8) than those younger. Of the various factors influencing mortality (low body mass index, being single, presence of one or more co-morbid disease, occurrence of cervical hip fracture and low mental score (<8.0)) only residence in institutional care prior to admission, presence of a co-morbid condition and poor "pre-fracture" functional status attained statistical significance. The hazards ratio associated with nursing and residential home residence were 2.1 and 1.7 respectively. Presence of one or more co-morbid disease increased the risk of death nearly 3-fold (HR=2.8). Similarly, one unit increase in health assessment score (i.e. poorer score) was associated with a 60% increased risk of death HR=1.6, (95%CI 1.2, 2.1). A higher physical component score (i.e. better quality of life) was protective HR=0.95 (95%CI 0.93, 0.98). Multiple regression analysis confirmed the importance of age at the time of hip fracture and physical function before fracture as the most important determinants of outcome in this group of elderly men (HR 1.1 and 1.5 respectively).

In conclusion, mortality after hip fracture is high. The cause of death is unrelated to the fracture. The most important determinants of outcome are age and the individuals functional abilities at the time of fracture. Identification of this high mortality group on admission may help target closer medical supervision, and give realistic prognosis of outcome.

11.2 BACKGROUND

Hip fractures are a major public health problem. In the UK, the lifetime risk for sustaining hip fracture from age 50- years is 18% in women and 6% in men. Excess mortality varies after hip fracture with 12-month rates varying from 12%-35% (Keene *et al*, 1993).

The incidence of hip fracture in men is about one third that in women, however, the available evidence would suggest the sequelae of hip fracture may be more serious in men. In particular several studies have suggested that mortality is greater than that observed in women. The reason for this excess in men is unclear. In part it may be related to co-morbid factors which both increase the risk of death and hip fracture (Poor *et al*, 1995).

There are few studies that have specifically looked at the effect of pre-fracture health status on the observed excess mortality of these patients. The role of co-morbid factors in predicting death is unclear (Poor *et al*, 1995; Myers *et al*, 1991; Jencks *et al*, 1988). The majority of studies report mortality in total not separately by gender.

The aim of this section is to examine mortality in a group of men with hip fracture, compare it with a comparable group of elderly men without a hip fracture living in the community and to determine factors which predict death post fracture including pre-morbid factors. Such data may help in identifying high-risk groups and help target specific preventive interventions.

11.3 PATIENTS AND METHOD

A case-control study with prospective follow-up of both groups for 2 years was designed. During the period 1995-97, 100 men aged 50 years and over consecutively admitted with a low trauma hip fracture were recruited as cases. In parallel, 100 men living in the community were randomly selected from a local general practice register as controls.

All 100 men with hip fracture consented to take part. To recruit 100 controls 185 men were invited to take part - participation rate 54%. All study subjects completed an interviewer-administered questionnaire. Where information could not be obtained directly from the subject it was obtained from a proxy relative or carer. First assessment was carried out at the time of the first visit in controls and within 48 hours of admission

in fracture cases. Information collected included demographic profile, residence prior to fracture (response set: own home / residential home / nursing home), mini-mental status, various co-morbid factors (including dementia, Parkinson's', heart disease, arthritis, diabetes, stroke, dementia, gut disorders, and osteoarthritis) and functional capacity using an 8 item questionnaire derived from the MEDOS and scored based on the health assessment questionnaire, termed health assessment score (for details see chapter 10). In addition quality of life 4 weeks prior to fracture was ascertained using the SF-36. The "physical component score" and " mental component score" were calculated in a standardised manner as described in the previous chapter.

All subjects were reassessed at 6 months, 12 months and 24 months. Vital status, information about their current place of residence and current functional ability was collected by direct contact with the patient, relative or carer using similar questionnaires. The cause of death was confirmed using death certificates or post-mortem reports obtained using the vital registration system from the registrar general office.

Statistical analysis: The pre and post fracture events at various time intervals were analysed using cross-tabulation procedures. The impact of various predictors of hip fracture on outcome was assessed using Kaplan Meier curves with log rank tests. Cox regression analysis was used to assess the predictive risk of the various confounding factors. In each case adjustment for age was carried out. Multiple cox regression analysis was used to assess the individual contribution of each risk factor identified. Analysis for hazards ratio was undertaken using STATA.

11.4 RESULTS

100 men with hip fracture, mean age 79.9 years (SD=9.4), and 100 controls, mean age 75.1 (SD=9.6) were studied. The baseline characteristics of both cases and controls are outlined in Table 11.1. Men with a hip fracture were more likely to be older, living in institutional care, have co-morbid diseases and greater functional impairment on admission than those without a hip fracture.

11.4.1 Differences in mortality between Cases and Controls

Subjects were followed for a mean of 661 days (1.8 years) (range 2-1128 days). Follow-up was 100% in both groups. In total there were 60 deaths among the fracture cases and 10 deaths among the controls (Table 11.2). Amongst cases early mortality (90 days) was

25%; more deaths occurred in the first year (45%) than in the second year (15%). Only one death was observed amongst controls in the first year, 9 more died by the end of the follow-up period.

Table 11.1 Baseline characteristics of Cases and Controls

At Baseline		No.	Cases	No.	Controls	Significance
Age (years)		100	79.9 (9.4)	100	75.1 (9.6)	<0.001
Residence	Own Home	100	71	100	96	$\chi2$=22.7, df=2,
	Residential H		14		2	p<0.000
	Nursing Home		15		2	
Co-morbidity	None	96	17 (18%)	94	40 (43%)	$\chi2$=22.4, df=2,
	Less than 3		32 (33%)		36 (38%)	p<0.000
	3 or more		47 (49%)		18 (19%)	
Physical Component Score	Baseline	81	38.9 (11.8)	100	46 (10)	<0.000
Health Assessment Score	Baseline	91	0.83 (0.85)	99	0.27 (0.51)	<0.000
Mental Component Score	Baseline	81	50.1 (12.6)	100	56.6 (8.1)	<0.000

Table 11.2 Outcome over 2 years in cases and controls

Outcome		Initially	3 months	6 months	12 months	24 months
Dead	Cases	-	25	31	45	60
	Controls	-	-	-	1	10
In hospital/nursing H	Cases	15	-	20	14	8
	Controls	2	-	2	2	2
In residential home	Cases	14	-	7	6	4
	Controls	2	-	3	3	2
In own home	Cases	71	-	38	36	30
	Controls	96	-	94	89	87

11.4.2 Factors influencing mortality in men with hip fracture

Figure 11.1 presents the Kaplan Meier survival curve for the two groups. Deaths amongst hip fracture cases were more frequent than in the controls, and the rate was most marked in the first 3 months following fracture, with rates declining subsequent to this. The overall survival amongst the cases was 36.5% compared to 87.7% amongst

controls (log rank test 62.6, df=1, p=0.000). Using cox regression analysis mortality was significantly higher in men with a hip fracture compared to the controls [Hazards ratio (HR) 9.3 (95%CI 4.8,16.3); p<0.000] see Table 11.3. The excess mortality persisted after adjusting for age [HR (95%CI): 8.1(4.1, 16.0)]; and subsequently for body mass index [HR (95%CI): 7.8(3.6, 16.9)]. Similarly, despite controlling for "pre-fracture" quality of life (using either the physical component or health assessment scores) men with hip fracture continued to exhibit a 6-7 fold excess risk of dying compared to the controls (HR 6.2-7.2).

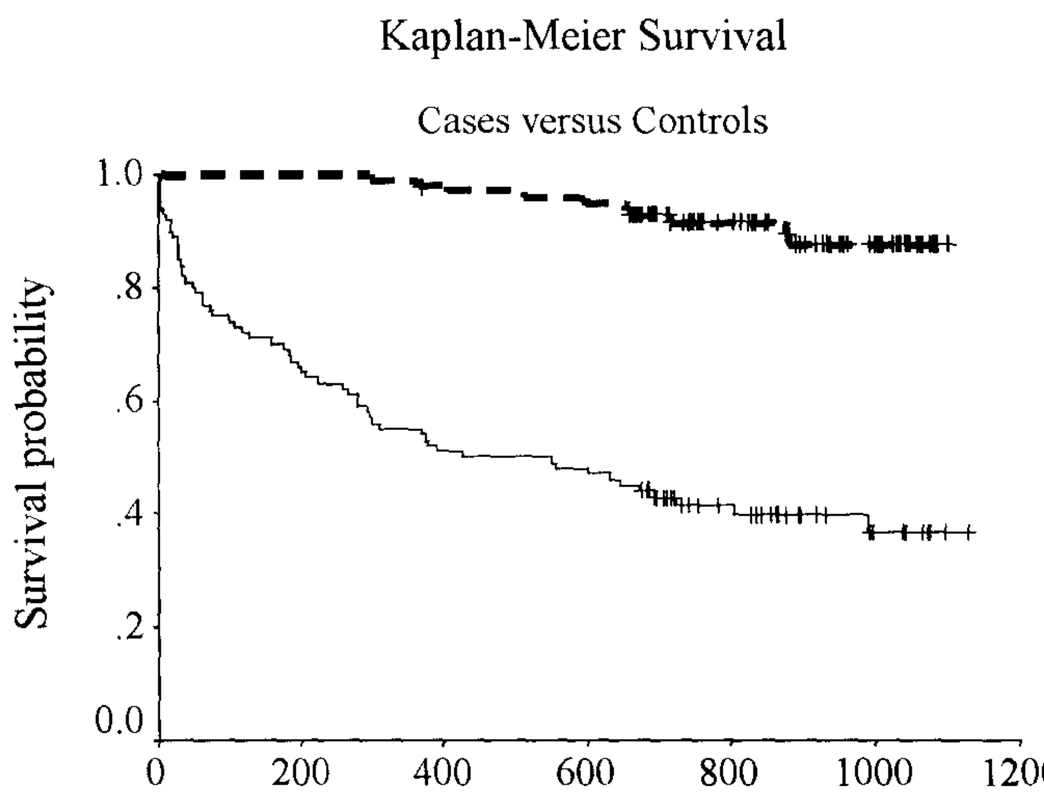


Figure 11.1 Kaplan-Meier Survival Curves amongst cases and controls

Cases ——; Controls - - - -

Table 11.3 Cox regression analysis for risk of death: cases versus controls

	Hazards Ratio (95%CI)	Significance
Presence of hip fracture	9.3 (4.8, 16.3)	0.000
Adjusted for age	8.1 (4.1, 16.0)	0.000
Adjusted for age and BMI	7.8 (3.6, 16.9)	0.000
Adjusted for age & baseline functional capacity (HAS)	6.7 (3.4, 13.4)	0.000
Adjusted for age & baseline physical component score (PCS)	6.2 (3.1, 12.4)	0.000
Adjusted for age & baseline mental component score (MCS)	7.2 (3.5, 14.7)	0.000

Figures 11.2-11.10 present Kaplan Meier curves looking at survival among hip fracture cases, according to their age (by decade), fracture type, residence on admission, marital status, presence or absence of co-morbidity body mass index, mental score and also their functional status. Detailed analysis of the survival curves is given as footnotes under each figure. Age was the single most important determinant of mortality. For each year increase in age the risk of dying increased by 10% (HR 1.1, 95%CI 1.0, 1.1) see Table 11.4. Compared to men aged less than 70 years those older were at 6 fold higher risk of dying simply due to age (HR 5.8, 95%CI 1.8, 18.4).

Table 11.4 Cox regression analysis for factors influencing mortality amongst cases

	Hazards Ratio (95%CI)	**Hazards Ratio* (95%CI)**	**Significance♣**
Age (for each year increase in age)	1.1 (1.0, 1.1)		0.000
Age (>70 years)	5.8 (1.8, 18.4)	-	0.003
Body mass index (per kg/m^2)	0.98 (0.89, 1.1)	1.0 (0.9, 1.1)	NS
Marital status: single Vs married	1.3 (0.8, 2.1)	1.2 (0.7, 1.9)	NS
Presence of one or more co-morbidity	4.2 (1.5, 11.7)♠	2.8 (1.0, 7.7)	0.05
Fracture type: cervical Vs trochanteric	1.3 (0.8, 2.2)	1.1 (0.7, 1.9)	NS
Mental score: <8.0 Vs 8 and above	1.8 (1.0, 3.2)+	1.5 (0.9, 2.6)	NS
Residence: Residential Vs Own home	2.1 (1.1, 4.1)•	1.7 (0.8, 3.3)	NS
Residence: Nursing Vs Own home	2.0 (1.1, 3.9)	2.1 (1.1, 4.0)	0.03
Physical Component Score (per unit change)	0.95 (0.93, 0.98)	0.95 (0.93, 0.98)	0.002
Functional Capacity (per unit change in HAS)	1.5 (1.1, 2.1)	1.6 (1.2, 2.1)	0.004
Mental Component Score (per unit change)	1.0 (0.98, 1.0)	1.0 (0.98, 1.0)	NS

* After adjusting for age; ♣ both unadjusted and after adjusting for age;
♠ $p<0.005$; + $p<0.04$; • $p<0.03$

Of the various factors evaluated, after adjusting for age (using cox regression analysis) only institutional care at the time of hip fracture, presence of a co-morbidity and poor

"pre-fracture" physical function were found to be significantly predictive of mortality (Table 11.4). Presence of one or more co-morbid disease at the time of the hip fracture more than doubled the risk of dying (HR=2.8). There was a gradient effect with hazards ratio paralleling the number of co-morbid diseases present (HR=2.7 if number of co-morbidities <3; HR=2.8 if no. of co-morbidities >3- data not shown). Mental score of less than 8.0 on admission was associated with a 50% increase in risk of death (HR=1.5) but did not reach statistical significance. Similarly, a 30% increase in mortality was seen in those single (versus married) or with a cervical fracture (compared to inter-trochanteric hip fracture) with hazards ratio of 1.3 each (Table 11.4). A higher physical component score was protective HR=0.95 (95%CI 0.93, 0.98); p<0.002. Men in the highest tertile of physical component score had 70% reduced chance of death (HR=0.30 95%CI 0.14, 0.65; p<0.002); those in the middle tertile 60% reduction (HR 0.39 95%CI 0.19, 0.80; p<0.01) compared to men in the lowest tertile (Table 11.5a). Repeat analysis was carried out in a similar manner assessing risk associated with poor "prefracture" functional capacity assessed using the health assessment score. A similar gradient effect was seen with a higher hazard ratio associated with a poorer score (score range 0-3; 0=best and 3=worst) see Table 11.5b.

Table 11.5a Cox regression analysis: Baseline Physical Component Score as a factor influencing mortality amongst Cases

	Hazards Ratio	S.E	Significance	95% CI
Age	1.1	0.02	0.000	1.1, 1.1
PCS lowest tertile	Referent	-	-	-
PCS middle tertile	0.39	0.14	0.01	0.19, 0.80
PCS highest tertile	0.30	0.12	0.002	0.14, 0.65

PCS: Physical Component Score (mean 33.4, minimum 14.9, maximum 63.3)
Lowest tertile: 14.9-32.8; Middle tertile: 32.9-44.5; Highest tertile: 44.6-63.3

Table 11.5b Cox regression analysis: Baseline Health Assessment Score as a factor influencing mortality amongst Cases

		Hazards Ratio	S.E	Significance	95% CI
Age		1.1	0.02	0.000	1.1, 1.1
Health Assessment Score	0-0.9	Referent	-	-	-
	1-1.9	1.97	0.65	0.04	1.0, 3.8
	2-3	2.58	0.98	0.01	1.2, 5.4

Using stepwise multiple regression with age, functional capacity and residence into the equation, the former two variables (i.e. age and functional capacity) were good predictors of the excess mortality with hazards ratios of 1.1 and 1.5 respectively (Table 11.6a). On adding co-morbidity to the regression equation the only significant variable influencing mortality was age see foot note Table 11.6a. On substituting a cut-off of 70 years for age into the above regression equation, the significance of age on mortality was even more apparent with HR=4.6 95%CI 1.4, 15.0; p<0.01. As a result, baseline functional capacity no longer retained its significance [HR 1.3 (95%CI 0.9, 1.8); p=NS) see foot note table 11.6a. Repeat analysis replacing functional capacity (Health Assessment Score) with the physical component score (PCS) did not alter the results (Table 11.6b). Age and baseline physical component score were the only two variables that significantly influenced mortality; age being the dominant of the two.

Table 11.6a Multiple Cox regression analysis for factors found to significantly influence mortality amongst fracture cases

	Hazards Ratio	**S.E**	**Significance**	**95% CI**
Age*	1.1	0.02	0.000	1.1, 1.1
Functional capacity at baseline	1.5	0.27	0.04	1.0, 2.1
Living in Residential Home	1.1	0.48	NS	0.5, 2.6
Living in Nursing Home	1.4	0.59	NS	0.6, 3.2

On adding co-morbidity to the equation: age HR=1.1 (95%CI 1.1, 1.1) p<0.000; Functional capacity HR 1.4 (95%CI 0.97, 2.0) p=NS; Residence p=NS

* Age over 70 years: HR 4.6 (1.4, 15.0), p<0.01; Functional capacity HR 1.3 (0.9, 1.8), p=NS; Residence =NS

Table 11.6b Multiple Cox regression analysis for factors found to significantly influence mortality amongst fracture cases

	Hazards Ratio	**S.E**	**Significance**	**95% CI**
Age*	1.1	0.02	0.000	1.0, 1.1
Physical Component Score	0.96	0.02	0.006	0.93, 0.99
Living in Residential Home	1.5	0.71	NS	0.56, 3.8
Living in Nursing Home	1.2	0.55	NS	0.52, 3.0

On adding co-morbidity to the equation age p<0.000; PCS p<0.01, residence and Co-morbidity =NS

11.4.3 Causes of death in Cases and Controls

A comparison between cause of death in both cases and control is shown in table 11.7. Common cause of death were chest infection amongst the controls (n=4) and both chest infection (n=21) and heart disease (n=17) in cases. Table 11.7b presents a cross tabulation of the cause of death amongst cases according to time of death since fracture. No differences were noted with bronchopneumonia and heart disease most common at all assessment intervals.

Table 11.7a Cause of death amongst cases and controls

Cause of death	Cases (n=60)	Controls (n=10)
Bronchopneumonia	21	4
Heart Failure	9	0
Ischaemic heart disease	8	1
Pulmonary embolism	2	0
Cerebrovascular accident	4	0
Malignancy	5*	1
Old age/ dementia	2	1
Infections	4♣	0
Others	5•	3♠

*Malignancy (n=5): prostate (3), stomach (1), unknown (1)

♣Infections (n=4): septicaemia following gangrene heel (1), GI obstruction (1), gastric ulcer (1), pseudomembranous colitis (1)

•Others (n=5): Small bowel ischaemia (2), GI bleed (1), Parkinson's (1), Carbon monoxide poisoning (1)

♠Others 9n=3): Respiratory arrest due to COAD (n=1), Spinal cord compression at C4 (n=1), rupture abdominal aortic aneurysm (n=1)

Table 11.7b Cause of death in hip fracture cases

Cause of death	Early (< 1 month)	Intermediate (1- 6 months)	Late (>6 months)
Bronchopneumonia	6	9	6
Heart Failure	2	-	7
Ischaemic heart disease	3	3	2
Pulmonary embolism	1	1	-
Cerebrovascular accident	1	-	3
Infections	1	-	3
Malignancy	-	1	4
Others	1	2	4

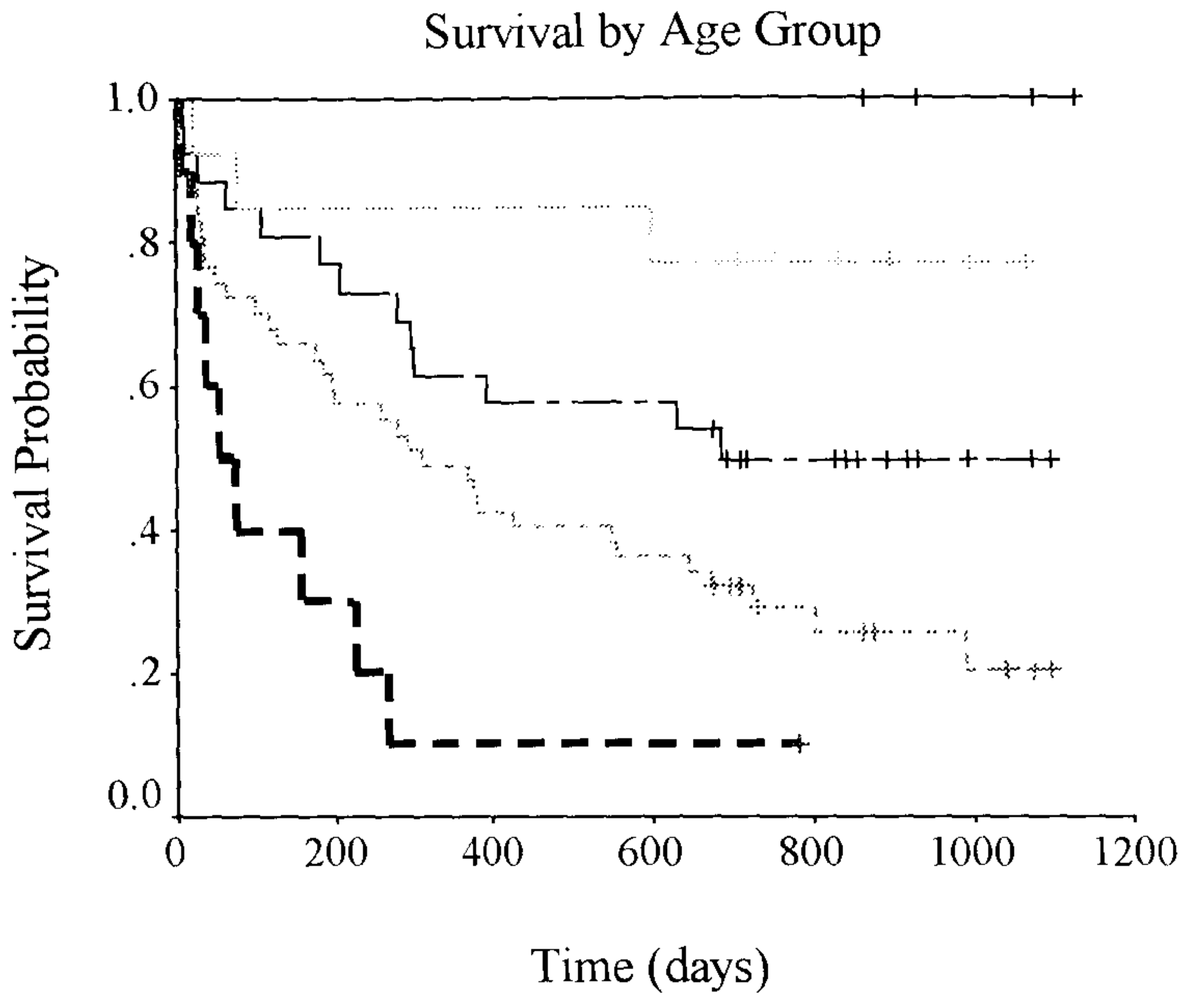


Figure 11.2 K-Meier Survival curves stratified by age group (in decade)

**50-59 —— ; 60-69 ..... ; 70-79 -.-.-.-

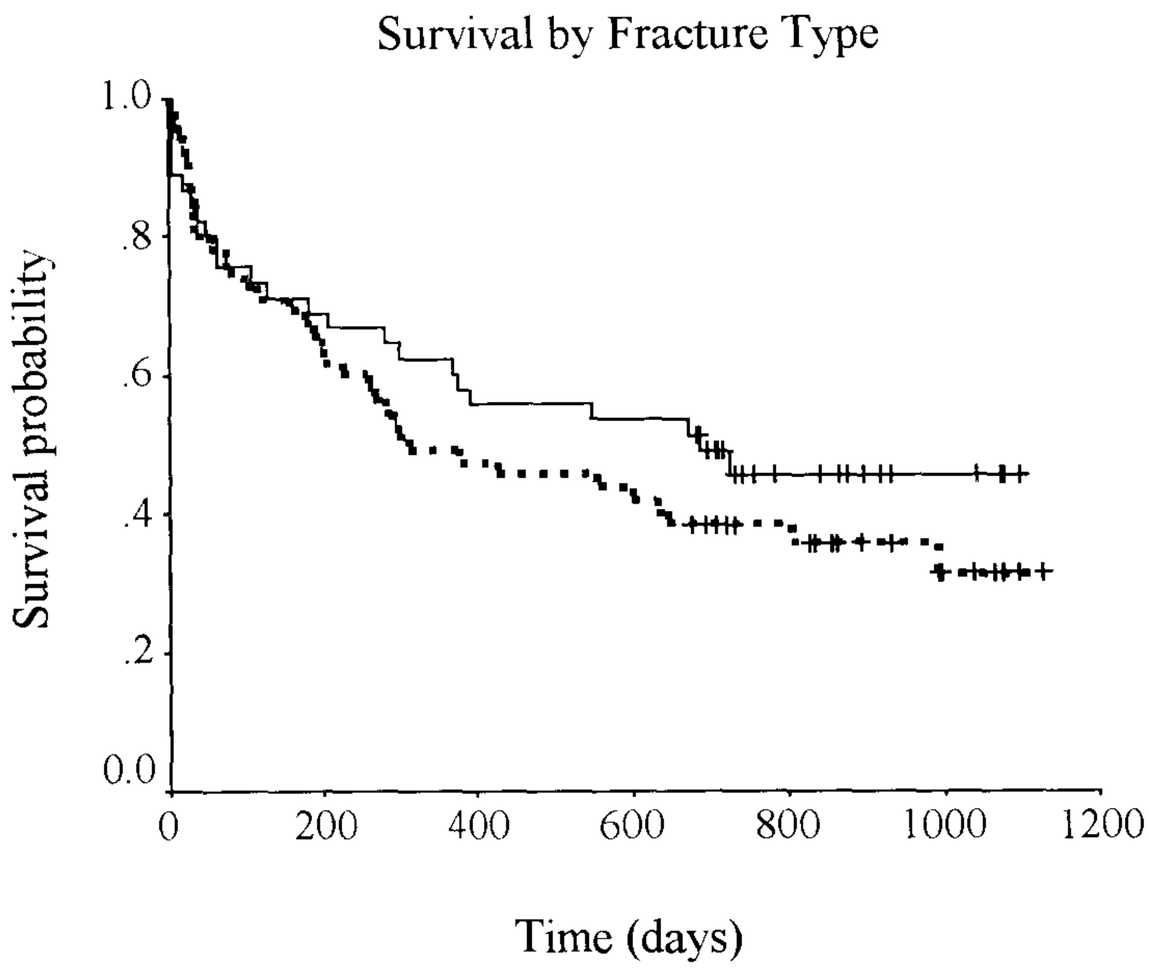


Figure 11.3 K-Meier Survival stratified by type of fracture: Inter-trochanteric versus Cervical fracture

Inter-trochanteric fracture —— ; Cervical fracture -----

The study comprised of 55 cervical and 45 intertrochanteric hip fractures. By the end of the follow-up (1128 days) there were 36 (65.5%) deaths in the cervical fracture group and 24 (53.3%) in those with an inter-trochanteric fracture. Overall there was no statistical difference in survival between the two groups (log rank test 1.2, df=1, p=0.31). There was no difference in mortality in the first 6 months; survival 67.3% in men with a cervical hip fracture and 68.9% in those with an inter-trochanteric fracture. However, by 1 year there were more deaths in men with a cervical fracture compared to fracture at the inter-trochanteric region (survival 49.1% and 62.2% respectively). This excess mortality in men with a cervical fracture persisted with survival figures being 38.2% and 45.4% respectively at 2 years. Interestingly, no further deaths were seen amongst patients with an inter-trochanteric fracture after 2 years (727 days). By 3 years (1128 days) men with cervical fracture experienced approximately a 15% higher mortality compared to those with an inter-trochanteric hip fracture.

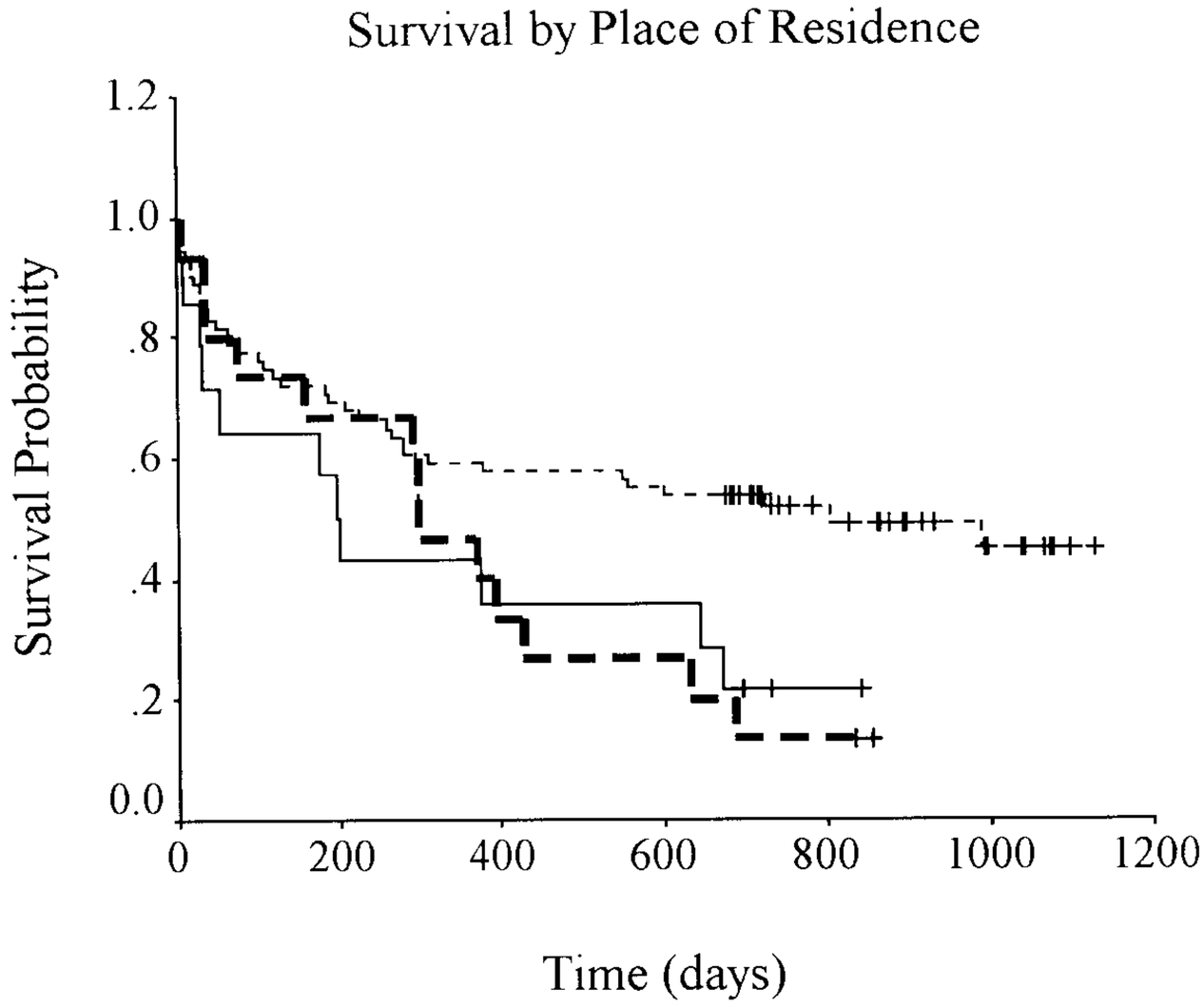


Figure 11.4 K-Meier Survival Curves according to place of residence on admission

Own home -----; Residential Home ____ ; Nursing Home _ _ _

Men living in their own homes before the hip fracture showed a gradually progressive down-hill course with cumulative survival of 84.5% at 1 month, 80.3% at 2 months, 70.4% at 6 months, 59.2% at 1 year, 51.5 at 2 years and 45.1% at 3 years. In contrast, men admitted from a residential home exhibited a very high mortality immediately after the fracture (28.6%) in 31 days (survival 71.4%). Mortality increased to 50% in just over 6 months (200 days) and was 78.6% (survival 21.4% only) in less than 2 years (675 days). Interestingly, men who fractured in a nursing home had the lowest mortality in the first month after the hip fracture (6.7% mortality i.e. survival 93.3% in 31 days). Their survival was better compared to men admitted from a residential home in the first 6 months (survival 66.7% in men from nursing home compared to 57.1% in men from residential home). However, by 1 year a reversal was seen with survival 46.7% in men from nursing home and 50% in those from residential home. This difference in survival was more marked at the end of 2 years with survival figures being 13.3% and 21.4% respectively. By the end of the follow-up period overall mortality was 54.9% in men admitted from home, 78.6% in men in residential home and 86.7% in men from nursing home (log rank test 7.7, df=2, p=0.02).

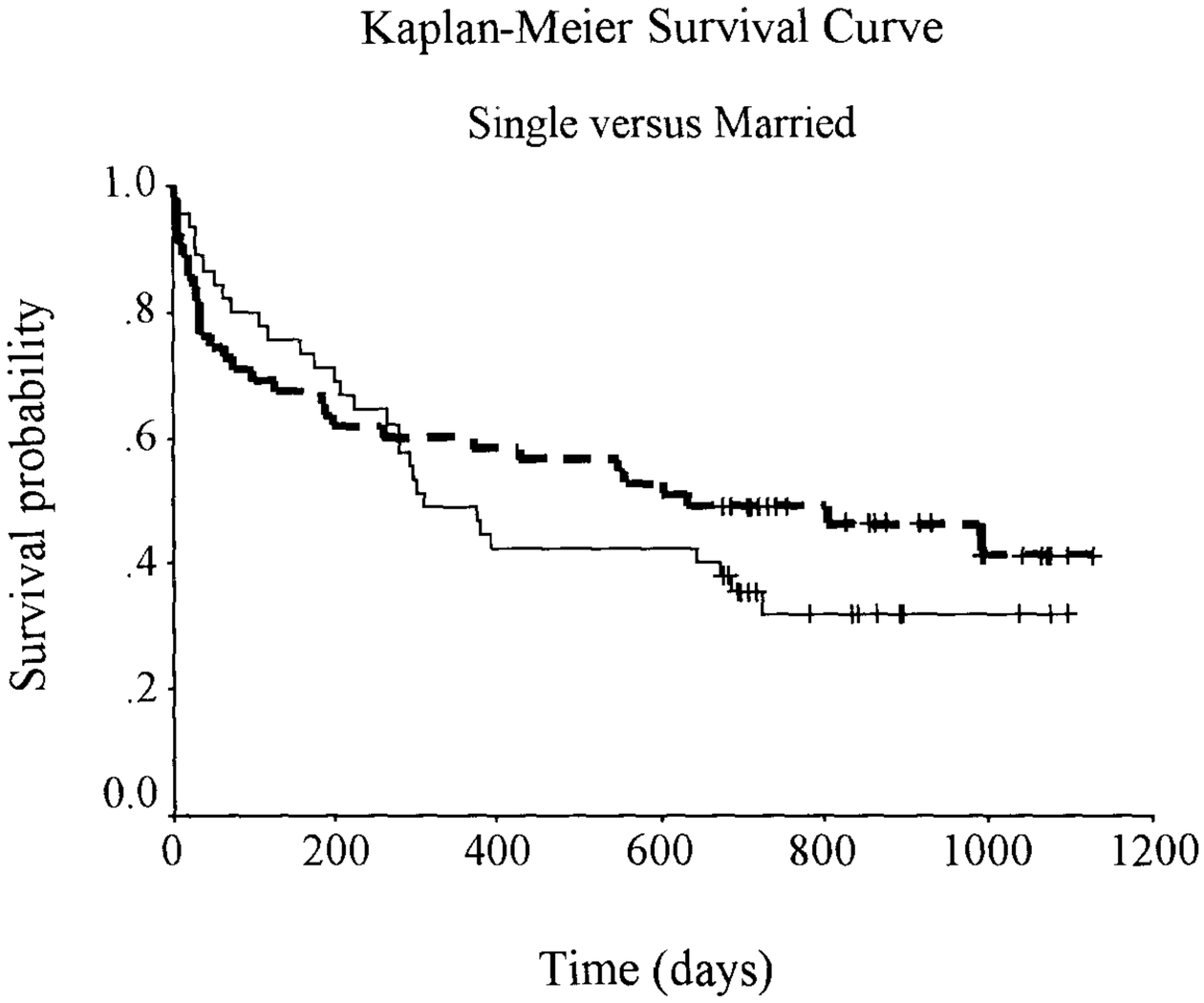


Figure 11.5 K-Meier survival curve by marital status

Married - - - - ; Single ——— (includes single, widowed, divorced, separated)

Mortality was high in both groups (single and married) in the initial few days following the hip fracture (cumulative survival: 88.9% and 81.8% in 30 days; 82.2% and 74.5% in 2 months amongst single and married cases respectively). Single men had a higher chance of survival compared to married men until 9 months when mortality in both groups became equal (mortality 40%, survival 60%). Thereafter single men continued to die at a steady rate but the death rate in married men declined such that a reversal was seen with the probability of survival amongst married men higher than those single. By 1 year survival dropped to 48.9% in single men compared to 60% in married men. These differences persisted and the survival probabilities were 31.7% and 49.1% respectively at 2 years. Despite continued deaths amongst married men and no further mortality in single men, the overall survival was lower (31.7%) in men who were single compared to 41.1% amongst those who were married at the time of the hip fracture (log rank test 0.8, df=1, p=0.37).

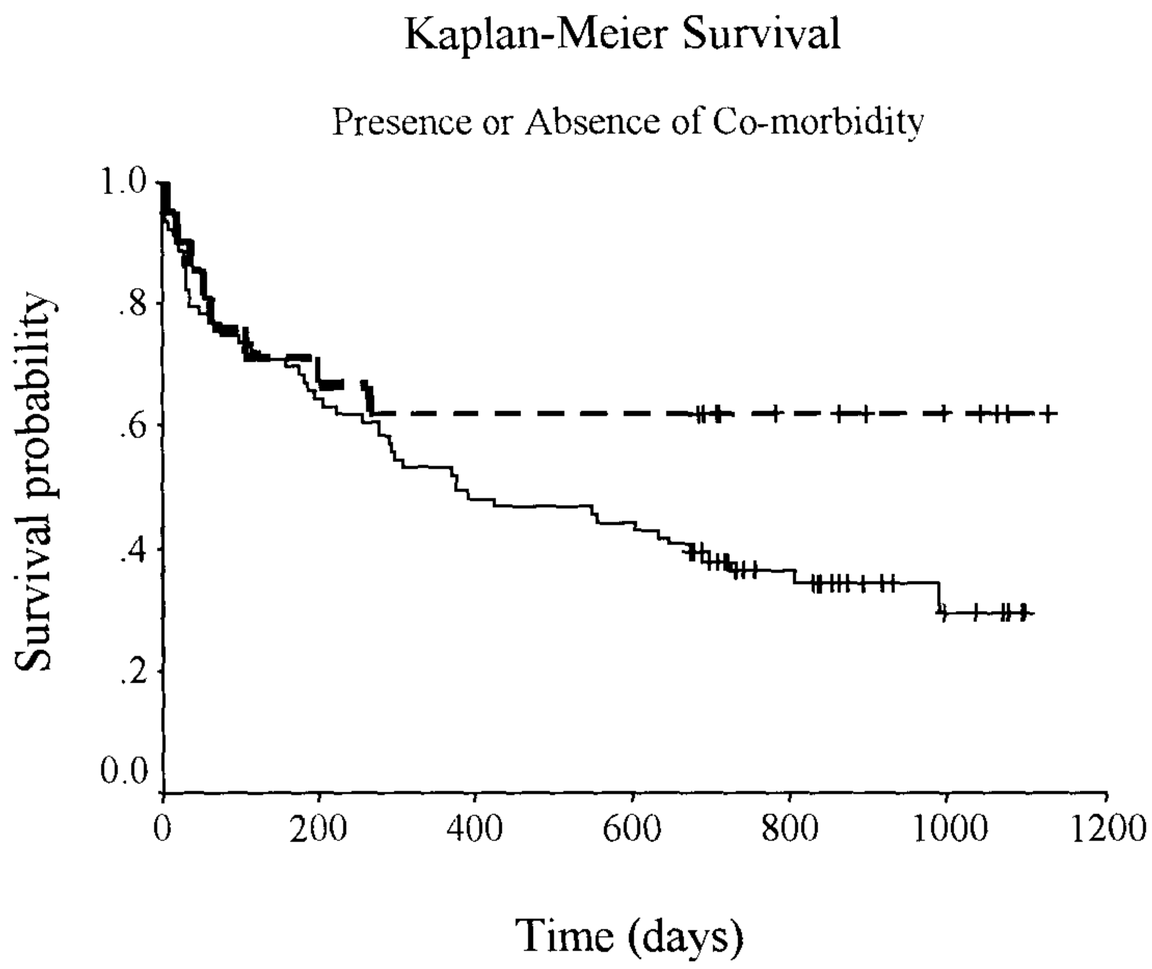


Figure 11.6 K-Meier survival curves in the presence or absence of a co-morbid condition

Absence of any co-morbidity - - - - ; Presence of one or more co-morbid disease ——

Men with one or more co-morbid condition showed a rapid and steady decline in survival from the time of hip fracture up to 14 months (427 days). Thereafter, mortality rate was less dramatic with cumulative survival by the end of the follow-up period of only 29.3%. For the initial 3 months, survival curves in men with hip fracture in the absence of any co-morbid condition were similar to those in men with a co-morbid disease (survival 76.2% versus 74.7% respectively). However, no further deaths were observed after 9 months (265 days) in men without a co-morbid disease. The overall mortality was over 70% (survival 29.3%) in the presence of any disease compared to less than 40% (survival 61.9%) in the absence of one (log rank test 3.3, df=1, p=0.07).

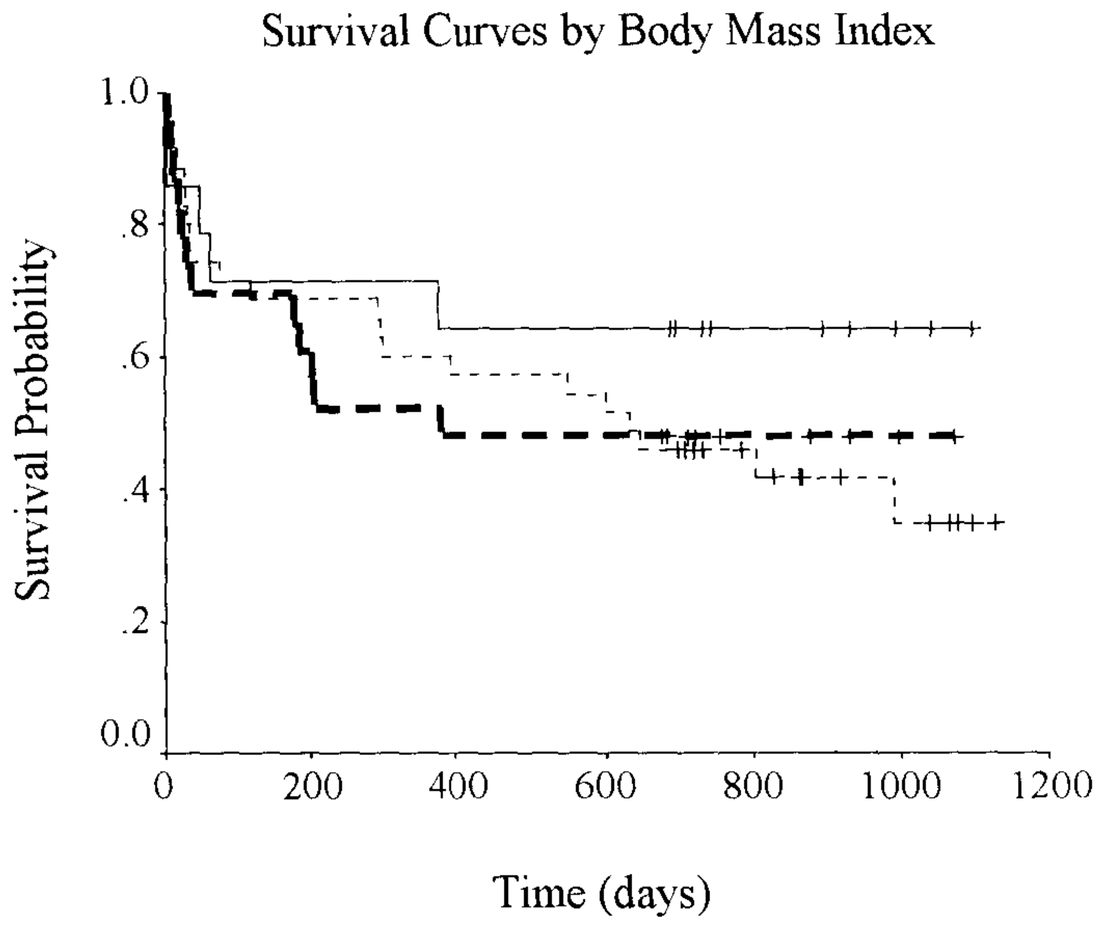


Figure 11.7 K-Meier Survival Curves according to Body Mass Index

BMI: lowest tertile ------- ; middle tertile — — —; highest tertile ——

Body mass index was divided into tertiles between the lowest and highest. Irrespective of body mass index mortality within first 2 months (61 days) was comparable in all 3 groups: 25.8%, 30.5% and 28.6% respectively amongst those in the lowest to the highest tertile. After 2 months cumulative survival in men in the lowest tertile of BMI continued to decline at a steady rate until 33 months after hip fracture with overall survival of only 34.6%. In contrast no further deaths were seen amongst men in both the middle and the highest tertile of BMI after just over a year (377 and 375 days respectively). The cumulative survival at the end of the observation period was 34.6%, 47.8% and 64.3% respectively in the lowest, middle and highest tertile (log rank test 1.4, df=2, p=0.50).

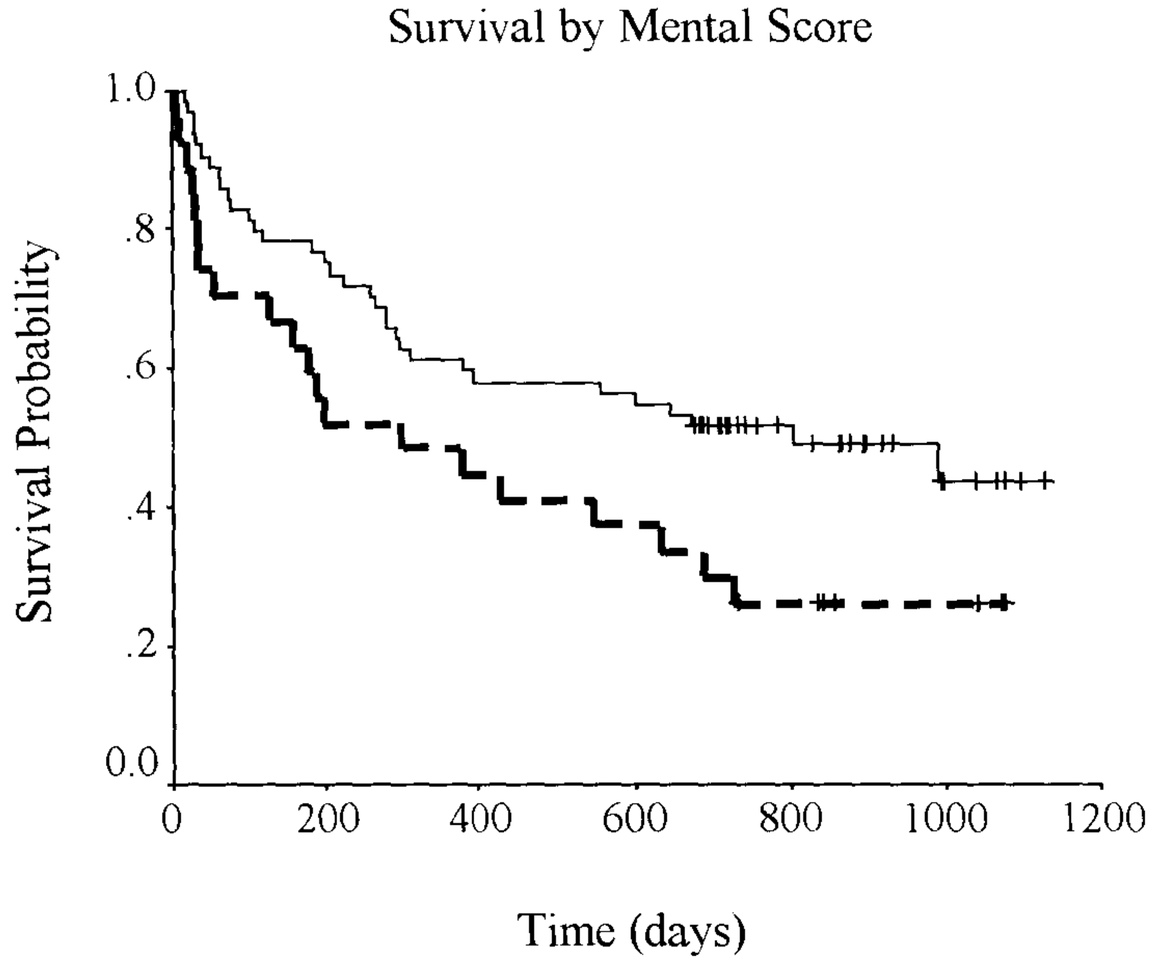


Figure 11.8 K-Meier Survival Curves based on Mental Scores

Mental Score equal to or more than 8 —— ; less than 8 - - - -

Mental score assessment was possible in only 91 of the 100 hip fracture cases. 64 (70.3%) scored 8 or more on a mental score scale of 0-10. Men with scores of less than 8 showed a very high mortality within 60 days of the fracture. The survival was 70.4% in men with low scores compared to 89.1% in men with higher scores (more than or equal to 8). A steady decline in survival was observed in both groups, although, at each time point men with low scores had a higher mortality compared to those with high scores. The survival figures were 59.3% versus 78.1% at 6 months, 48.2% versus 60.9% at 1 year and 25.9% versus 51.6% at 2 years. By the end of the follow-up period only a quarter of men with low scores survived (mortality 74.1%) compared to over 50% (survival 51.6%) in those with high scores. This difference in mortality was statistically significant (log rank test 4.5, df=1, p=0.03).

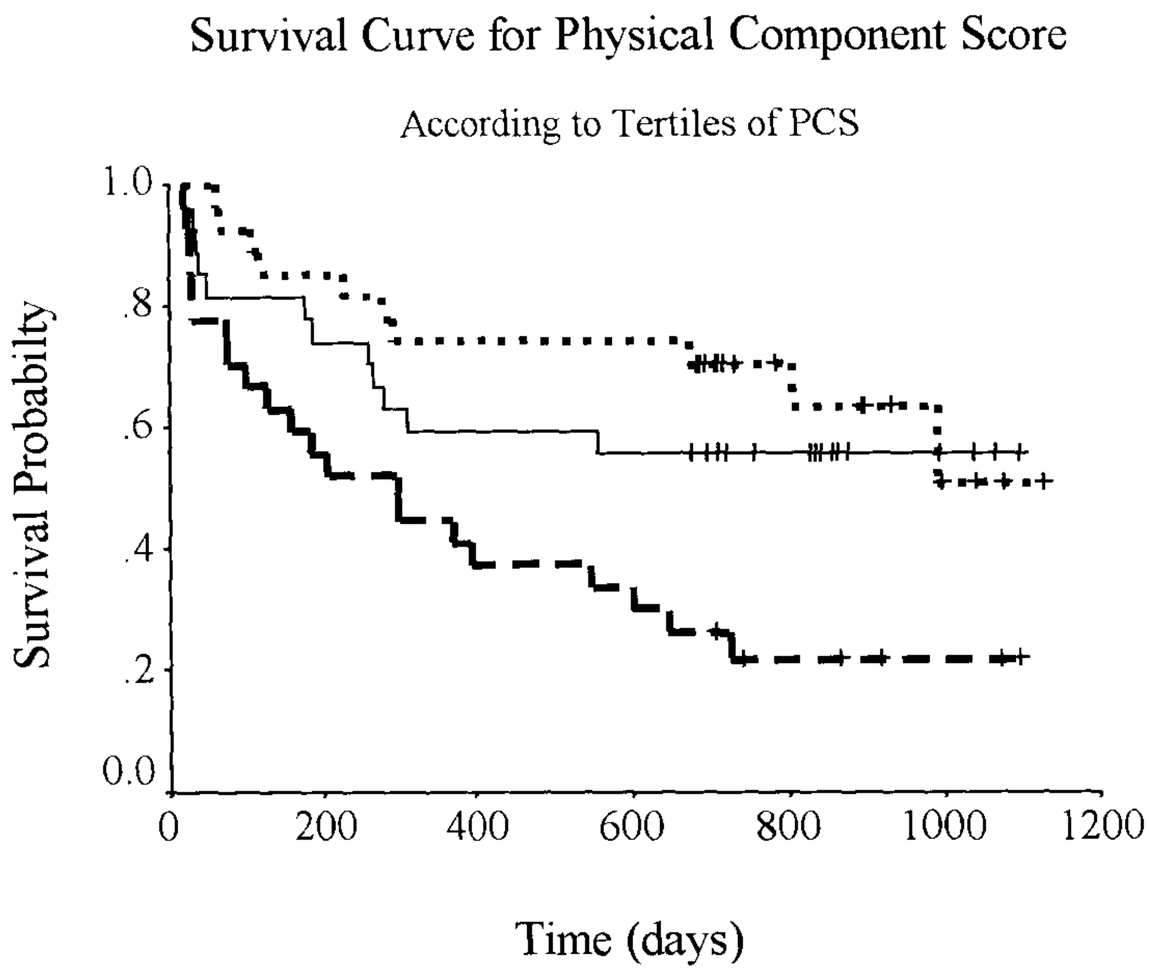


Figure 11.9 K Meier Survival Curves stratified by PCS: Physical Component Score

14.9 - 32.8 - - - - ; 32.9 - 44.5 ——— ; 44.6 -63.3 .....

The Physical Component Score was derived from the SF-36 questionnaire using standard techniques. The mean PCS in the 81 cases where it was scored was 33.4 with a range between 14.9-63.3. Subjects were divided according to tertiles of PCS: lowest between 14.9-32.8; intermediate 32.9-44.5 and highest 44.6-63.3. A higher score signified better functional ability and independence. Interesting 27 subjects each fell into either group. 21 among the lowest tertile, 12 of the intermediate and 10 of the highest tertile died at the end of the observation period. Mortality amongst men with the lowest scores was evident from the immediate post fracture period with survival reduced to 78% at 1 month, 44% by 1 year and 21.6% by 2 years. Men with the highest (best) scores exhibited no deaths within the first two months post-fracture. The survival at 1 year was 74% with only one more death in the second year reducing the survival to 70.4% at 2 years. Two further deaths reduced the final survival to 50.7% (mortality 49.3%). Men with intermediate scores exhibited early mortality with survival reduced to 81.5% in 2 months (47 days) and all but one death occurring in the first year with survival of 59.3% at 2 years. Due to only one extra death in the second year the cumulative survival at the end of the observation period amongst men in the intermediate tertile (55.6%) was better than men with the higher (better) scores (50.7%). The difference in survival between the three groups was statistically significant: log rank test 11.6, df=2, p=0.003.

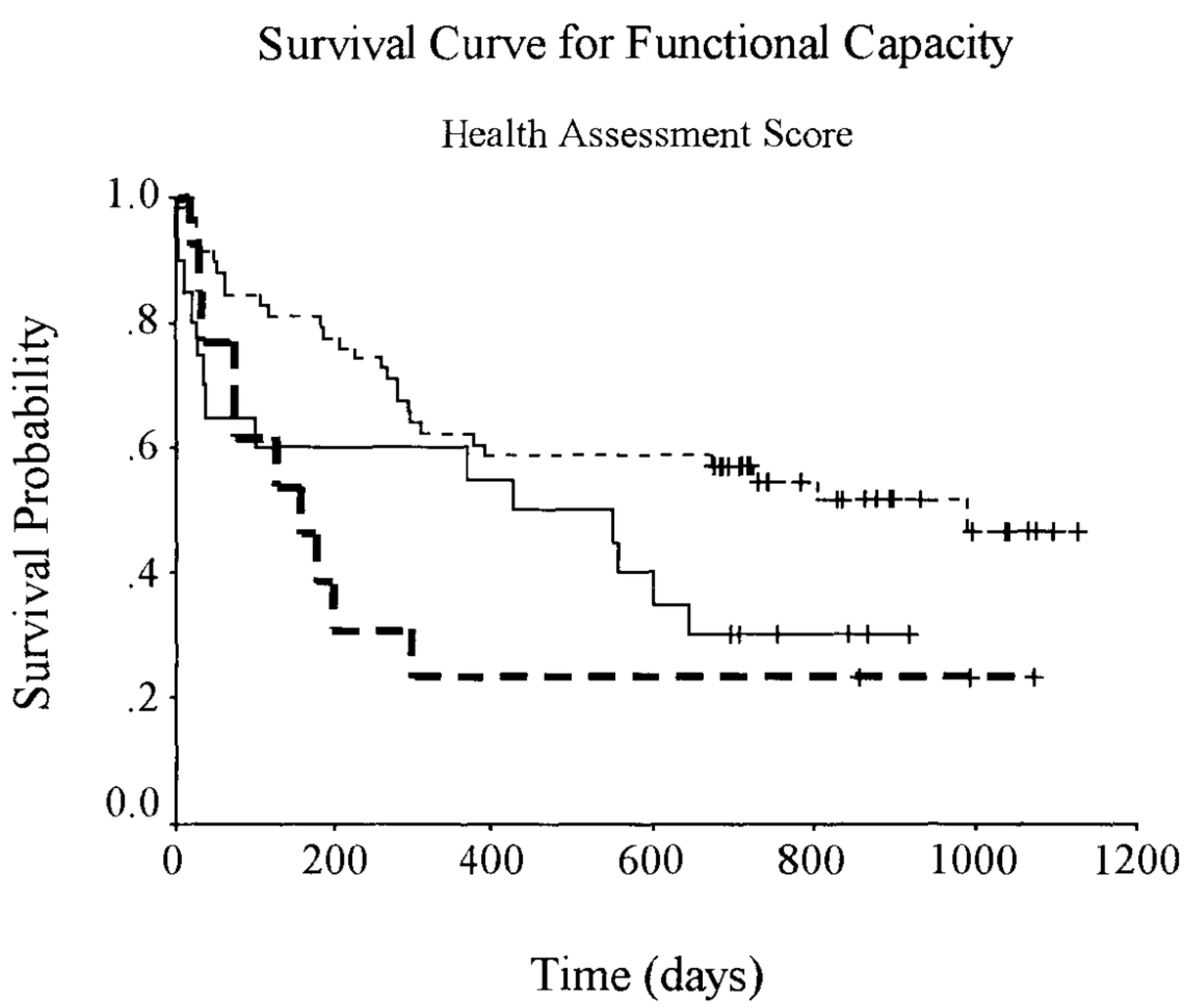


Figure 11.10 K Meier Survival Curve based on Health Assessment Score (Range 0-3)

0-0.9 - - - - ; 1-1.9 —— ; 2-3 - - - - -

Functional capacity was assessed using Health Assessment Score range 0-3, with 0= best and 3 worst functional ability. 91 of the 100 fracture cases completed the questionnaire: 58 scored between 0-0.9, 20 scored between 1-1.9 and 13 scored over 2. Survival was the best amongst men with the lowest score: 62% survival in the first year, 4 more deaths in the second year (survival 55%) and only two further deaths by the end of the follow-up with resultant survival of 46% (mortality 54%). Of the 20 men with intermediate scores 14 died, 8 within the first 3 months (98 days). There were no further deaths in the first year. The remaining 6 died in the second year of follow-up with overall survival of 30% (mortality 70%). All 13 men with the highest scores (range 2-3) died within the first year (298 days) with overall survival of only 23% (mortality 77%). The differences in survival seen between the 3 groups was statistically significant (log rank test 7.6, df=2, p=0.02).

11.5 CONCLUSION

Our fracture cases had a very high mortality; 60% were dead after 24 months with 31 deaths within 6 months of fracture. There were a wide variety of causes and most could not be directly related to the fracture. Bronchopneumonia and ischaemic heart disease were the commonest cause as would be expected in any elderly population. The previously reported mortality, with 16-37% of cases dying after fracture, probably under-estimates death by limiting follow-up to 12 months, excluding the very elderly by imposing upper age limits and excluding high risk cases who were admitted from

institutional care or have high dependency. This study has several advantages i) a case-control design, ii) controls representative of the community, iii) absence of an upper age limit, iv) inclusion of subjects irrespective of residence and degree of functional disability and v) complete follow-up of all study subjects in both groups over the entire study period. All contribute to the validity of the study results.

Presence of hip fracture was associated with over 9-fold increased risk of death compared to community controls. Our two study populations were not perfectly age matched. In addition there were significant differences in percentage requiring institutional care, number of co-morbidities and degree of functional disability at baseline. One could argue that the excess mortality noted amongst fracture cases is simply a reflection of these differences. However, the excess risk is still 6-8 fold after controlling for these variables.

A number of factors were identified as predictors of mortality after fracture. In parallel to the observations by previous researchers increasing age, low body mass index, poor mental score on admission and presence of a co-morbidity were associated with increased risk; however only age and co-morbidity were statistically significantly. The single most important factor was age with 10% higher risk per year increase in age. The effect of age was significant even after adjusting for the other variables in a multivariate analysis (per year increase in age HR=1.1, 95%CI 1.1, 1.1, $p<0.000$).

Men with hip fracture are almost all elderly and many are frail. Most workers have found co-morbidities as risk factors for high mortality (Poor *et al*, 1995, Nettleman *et al*, 1996, Stavrou *et al*, 1997, Aharonoff *et al*, 1997, Myers *et al*, 1991). Presence of any co-morbidity was associated with an increased risk of mortality in this group of men (HR=4.2). A gradient effect was observed with a higher hazards ratio associated with increasing number of co-morbidities (HR=2.7 if no. of co-morbidities <3; HR=2.8 if no of co-morbidities >3). However, due to small numbers the effect of individual co-morbid conditions was not evaluated. Moreover, in a multivariate model the overall influence of co-morbidity remained insignificant after adjusting for other predictors of death. The cause of death in these patients reflects the co-morbidities; they were similar to those in the control population. The causes of death were likely to be chest infection, ischaemic heart disease, malignancies, stroke and gastrointestinal diseases similar to those reported by Poor *et al*, 1995.

Only two studies have addressed the relation of fracture type on mortality (Poor *et al*, 1995 and Aharonoff *et al*, 1997) and both found no relation between the two. On the contrary, in this study, although statistically insignificant, men with a cervical hip fracture were at a higher risk with hazards ratio of 1.1-1.3 compared to men with an inter-trochanteric fracture. The number of fractures is small (55 and 45 respectively) and need caution before interpretation. Similarly the effect of marital status on outcome has not been addressed in previous studies in men. Men who were single were at greater risk of dying post fracture compared to their married counterparts. The only study addressing residence at the time of fracture as predictor of mortality (Poor *et al*, 1997) failed to show an association. On the contrary, in this study men living in institutional care at the time of the hip fracture had a 2-fold risk of dying compared to those living in their own homes. The difference in observation may be the small number of deaths (n=21) in the study by Poor and that data was collected from retrospective chart reviews and not by prospective follow-up.

Previous researchers have not studied the effect of "pre-fracture" health status on mortality. This study addressed the role of both the physical and mental component scores derived using the SF-36 on mortality. A higher PCS was protective with risk of death reduced by 5% per unit increase in the score (HR=0.95). Along the same lines, a higher (poorer) functional capacity score (HAS) was a risk factor with hazards ratio of 1.5. A higher pre-fracture PCS was protective with 70% reduction in risk of death (HR=0.30) amongst subjects in the highest tertile of the score. This finding was supported by observing over 2.5 fold increase in death amongst men in the highest tertile of functional capacity (poorer score) compared to those in the lowest (best) HR=2.58. The MCS had no influence (HR=1.0). After multivariate analysis in addition to age, pre-fracture physical functioning of the individual was the only significant predictor of mortality.

Hip fractures represent a significant source of mortality for the elderly population. Many determinants of outcome are independent of the level of care given and are dependent on pre-fracture functional status. It is important to point out that neither the immediate not long term mortality rates after hip fracture are attributable solely to the hip fracture- the cause of death being what would be expected in any elderly population. Thus, hip fracture is often not the sole factor leading to death and functional decline; rather it is the

cumulative effect of the hip fracture in the setting of advancing age, co-morbidities, poor general health and physical disabilities.

Patient's age, prefracture dependency in activities of daily living and presence of co-morbid conditions are all factors that are independent of treatment. This study provides prognostic information that can be shared with patients and their families. Knowledge of the probability of survival following hip fracture is of practical value when counselling patients and their families after the event. It also helps design measures to assess the impact they have on fracture outcome.

4. CONCLUSION

4.1 Summary

Using a population based case-control study design with prospective follow-up for two years this study has shown that low trauma hip fractures are common amongst Caucasian men in Cornwall (incidence 140/100,000/year) and are the result of low bone mineral density coupled with an increased risk of falls. Some of the variables that seem likely to have contributed to this "high risk" status are frailty (low body mass index), poor milk intake in childhood, limited mobility in adult life, poor general health (low SF-36 scores), presence of co-morbid diseases (Parkinson's, dementia, poor mobility, poor vision, frequent falls) subclinical vitamin D deficiency, low sex steroids (androgens and oestrogen's) and impaired osteoblast function with uncoupling of bone turnover.

The study also reveals that low trauma hip fracture in men is associated with significant morbidity and high mortality. Morbidity is evident by a high proportion in institutional care upto 2 years after the event, need for help with basic activities of daily living and poor scores using the SF36. The observed mortality of 45% and 60% at 1 and 2 years respectively, is unrelated to the fracture with chest infections and heart disease being the commonest cause.

The main findings of this study have been described in detail under separate headings in the "results" section of this thesis. An attempt has also been made to discuss the strengths and limitations of each finding and comparisons made with published literature. In the subsequent section an attempt is made to draw the findings together in a larger format and conclude with recommendations for future research. The sequence in which risk factors are discussed follows the pattern in which they appear in the "results" section of the thesis.

4.2 Incidence

Low trauma first hip fractures in elderly Caucasian males is common with an incidence of 140/100,000/year in Cornwall, which exceeds the only pre-existing UK incidence data on male hip fractures (114/100,000/year) from a 1985 study of 22 males in Oxford (Boyce and Vessey, 1985). The apparent rise in incidence reflects the rising world-wide incidence of hip fractures (Cooper *et al,* 1992; Kanis, 1993; Gullberg *et al,* 1997).

4.3 Risk Factors- Anthropometry, Lifestyle, BMD, Endocrine and Bone Markers

4.3.1 Anthropometry

In this study, men with hip fracture were lighter and had low body mass index. There were no differences in height. The relationship of *height* to risk of hip fracture has been studied by a number of workers (Meyer *et al,* 1993 & 1995; Hemenway *et al,* 1994; Poor *et al,* 1995; Nguyen *et al,* 1996; Grisso *et al,* 1997). Most studies have suggested taller height to be an independent risk factor for hip fracture (Meyer *et al,* 1993; Hemenway *et al,* 1994; Poor *et al,* 1995) with an odds ratio of 1.6 per 6 cm increase in height (Grisso *et al,* 1997). One possible explanation for this is the strong association of height with hip axis length, itself a risk factor for hip fracture. No difference was observed in hip axis length between the two groups in this study supporting the findings of similar height. Furthermore, it has been suggested that since height decreases with advancing age measurement of "current" height may not be as reliable as "peak" height in assessing the fracture risk of an individual. The cross sectional design of this study precluded such measurements.

The relationship between *weight* and risk of hip fracture has been studied using "current weight", "weight gain" and "weight loss" over defined periods and linking these to risk of hip fracture. All studies confirm low weight to be a risk factor (Nguyen *et al,* 1996; Langlois *et al,* 1998; Mussolino *et al,* 1998) supporting the observations in this study.

Although low *BMI* is a significant predictor of hip fracture risk in women it has not been consistently related to hip fracture risk in men. One reason for this discrepancy is the timing of the measurement in relation to the fracture. Studies using "current" anthropometric measurements have consistently shown low BMI to be a risk factor for hip fracture in men (Meyers *et al,* 1993; Grisso *et al,* 1997; Langlois *et al,* 1998; Burger *et al,* 1998). In contrast studies that have based calculations on "previous" weight (Felson *et al,* 1993; Hemenway *et al,* 1994) have failed to show the association. Findings from this study strengthen the importance of low body mass index as a potentially modifiable risk factor for low trauma hip fracture in men.

4.3.2 Lifestyle Risk Factors

Due to the study design and setting, this study was limited in studying the effects of *age* and *race* on risk of hip fracture in men.

The study showed that fracture risk was increased sevenfold in single men and fivefold in men living alone or in care. This is in keeping with the only previous report on men by Meyer and colleagues (Meyer *et al,* 1993) that "unmarried" and "divorced" states were significant risk factors for fracture.

The mother was the most common relative affected with osteoporosis in both groups. Maternal history of osteoporosis and or fracture is a well-recognised risk factor for osteoporosis in women. There is dearth of literature for men. The Rancho Bernado Study (Soroko *et al,* 1994) showed a significant relationship between maternal history of osteoporosis and lower BMD at the hip in men. The sample size of the current study may have meant small numbers of relatives to observe sizeable differences between the two study populations.

Walking for one hour each day decreased fracture risk by 74%. A protective effect was noticed with increasing duration of walking ranging from less than half an hour to over an hour each day (Odds Ratio 0.37-0.26). This supports the observations of previous workers reporting inactivity as a risk factor (Poor *et al,* 1995) and exercise decreasing fracture risk (Paganini-Hill *et al,* 1991; Nguyen *et al,* 1996; Grisso *et al,* 1997). The degree of protection conferred has been shown to be irrespective of type of activity (Grisso *et al,* 1997).

Lifestyle factors such as occupation, alcohol intake, and tea and coffee consumption were unrelated to fracture risk. Compared to never smokers, past versus current smokers were at increased risk of hip fracture but the results did not attain statistical significance (OR 1.35; 95%CI 0.54, 3.38 and OR 1.77 95%CI 0.58, 5.45). The effect of smoking on hip fracture risk in men is less clear. The Leisure World Study (Paganini-Hill *et al,* 1991) showed that fracture risk was associated with current smoking and that the risk for past smokers was not different from that of lifetime non-smokers. A recent meta-analysis of cigarette smoking, BMD and risk of hip fractures (Law and Hacksaw, 1997) have concluded similar effects on BMD and risk of hip fracture in both sexes. Results for alcohol have been varied in previous

prospective studies in men. Moderate alcohol consumption has been suggested to be associated with increased BMD (Glynn *et al,* 1995) and alcohol abuse with osteoporosis and increased fracture risk (Slemenda *et al,* 1992). In contrast two case-control studies did not find an association between current or past alcohol intake and risk of fracture despite a relatively high prevalence of heavy use (Grisso *et al,* 1991; Poor *et al,* 1995). Varying results for both alcohol and smoking may be due to the differences in the way in which these variables were measured. Poor recall relating the duration and extent of consumption of both products in this group of elderly men may have affected the study results.

Fracture risk was increased fourfold amongst those drinking less than one glass a week of milk in childhood. Studies in women have showed a relationship between low calcium intake and fractures (Cumming and Nevitt, 1997). However, the previous two studies addressing this in men did not show a significant relationship, probably due to the small number of hip fractures (21 & 31 respectively) in their study population (Nguyen *et al,* 1996; Mussolino *et al,* 1998). More recent studies addressing the relationship between diet, calcium and BMD in men have confirmed a positive correlation (Burger *et al,* 1998; Nguyen *et al,* 2000).

Compared to controls, cases exhibited poor overall health at the time of the fracture as suggested by low mean body mass index, low scores in most of the SF-36 domains and frequent co-morbidities. Some co-morbidities (Parkinson's disease, dementia, reduced mobility, poor vision and history of falls) increased the risk of fracture, possibly by increasing the risk of falls. Others including heart disease, osteoarthritis and diabetes had no effect. Almost all studies confirm the presence of co-morbid diseases as risk factors for hip fracture (Mussolino *et al,* 98). Using a case-control study design Poor and colleagues demonstrated significantly increased risk of hip fracture in association with Parkinson's (OR 8.0), dementia (OR 5.3), blindness (OR 5.5), vertigo (OR 6.0), hemiplegia (OR 2.6) or anaemia around the time of fracture (OR 2.6) (Poor *et al,* 1995). Similar results were obtained in another case-control study (Grisso *et al,* 1997). The authors demonstrated specific chronic illnesses (stroke, Parkinson's disease) as well as having two or more chronic illnesses to be associated with increased risk of fracture. An explanation for the association is the probable link between these disorders and secondary causes of osteoporosis or an increased likelihood of falling. The present and earlier studies focusing on fracture risks in

males underline the important links between ill health, concomitant co-morbidities, risk of falls and hip fracture. In the absence of any published data on quality of life in men with hip fracture this study is limited in making comparisons with other study populations.

4.3.3 Bone Mineral Density

This study identified several risk factors for fracture. The most obvious is low bone mineral density. Using the WHO definition of osteoporosis (t-score <2.5SD of young normal mean), and using the manufacturers (Hologic) normal value, 83% of fracture cases were osteoporotic at the femoral neck, and 36% at the lumbar spine (the corresponding figures for the controls were 39% and 5% respectively). After adjusting for age, height and weight, the risk of hip fracture increased for each standard deviation reduction in bone mass at all sites measured. The association was stronger for measurements at the proximal femur than the lumbar spine: lumbar spine (OR=1.8), femoral neck (OR=3.1). Bone mass, at all sites, was lower in those with an inter-trochanteric compared to those with cervical fractures, though the difference was significant for the trochanteric measurement site only. Although the link between bone mass and risk of hip fracture is well established in women (Marshall *et al,* 1996), there are few data in men and the number of study subjects is small (<40) (Karlsson *et al,* 1993; Greenspan *et al,* 1994 & 1998; Boonen *et al,* 1997; Nyquist *et al,* 1998; De Laet *et al,* 1998).

The magnitude of the risk of hip fracture associated with femoral neck BMD has been reported in several studies. Nguyen reported a 66% reduction in risk of hip fracture (n=31) per SD *increase* in BMD at the femoral neck (Nguyen *et al,* 1996), while De Laet (De Laet *et al,* 1998), reported a 3 fold increase in risk of fracture (n=23) associated per SD *decrease* in BMD. These data are similar to the findings in this study of a 3.1 fold increase in risk per SD *decrease* in femoral neck BMD.

In this study the strength of association between bone mass and fracture risk was greater for measurements at the hip than those at the spine. This may be in part due to the presence of concurrent degenerative disease which leads to an artifactual increase in spinal bone density (Masud *et al,* 1993; Jones *et al,* 1996).

Men with trochanteric fractures had lower bone mass at all skeletal sites compared to those who had sustained cervical fractures. The difference, however, was significant only for trochanteric BMD. Similar findings have been reported using the Singh Index in men (Sernbo *et al,* 1989) and DEXA in women (Karlsson *et al,* 1993; Greenspan *et al,* 1994). In contrast, however, to previous reports in women this study could not confirm a protective effect of femoral neck BMD (Greenspan *et al,* 1994).

There are certain limitations that need to be considered in interpreting these findings. Fracture cases were recruited consecutively, and none of those invited to participate declined. Controls were recruited from a local general practice, and a proportion of those invited (46%) declined to participate. If this was because they were less healthy and therefore likely to have lower bone mass than those who took part, the observed differences in BMD between fracture cases and controls may have been overestimated. An alternative strategy would have been to select the controls from a hospital population, however, such a group, because of concurrent illness may not be representative and it may be difficult to extrapolate the findings to the general population. It has been suggested that community controls comprise the more appropriate control group in case-control studies of hip fracture in the elderly (Moritz *et al,* 1997).

It is possible that observed differences are confounded with age. However, the use of a range of different analytic approaches suggests that this is not the case. Furthermore, all patients had BMD measurements within a maximum one week of the fracture (preferably 3-4 days). The observed low density cannot therefore be accounted for by immobilisation induced bone loss.

The frailty and poor mobility of cases immediately after the hip fracture caused difficulties in obtaining data concerning bone mass in a significant proportion (38%). Individuals in whom BMD was not assessed were older and a greater proportion had co-morbidities than those who were assessed - factors again likely to be linked with lower BMD. The effect of such selection bias, if present, would be to underestimate the strength of the relationship between hip fracture and BMD.

This study was cross-sectional - one of the major limitations with such a design is that it is not possible to determine the temporal nature of the observed associations. Prospective studies are required to determine the predictive risk of BMD in determining future fracture risk. In addition this study looked at a group of UK Caucasians - these findings may not necessarily be applicable to other racial/ethnic groups and /or in different study settings.

4.3.4 Hip Axis Length

Unlike previous published findings in women, this study did not find any association between hip axis length and hip fracture risk in men. In women an increase in hip axis length has been linked with hip fracture risk in several studies (Faulkner *et al,* 1993, Duboef *et al,* 1997). To the best of my knowledge there are no previous reports concerning the influence of HAL on fracture risk in men. Two previous studies suggested no difference in femoral neck axis length (one of the component parameters of HAL) among fracture cases than controls (Peacock *et al,* 1995), however, the link between FNAL and hip fracture risk is less clear (Karlsson *et al,* 1996, Center *et al,* 1998). The mechanism by which an increase in HAL confers an increase in susceptibility to fracture in women is unknown. Studies suggest that the risk persists after adjustment for body height and weight indicating it is not a surrogate for body size (itself linked with an increased risk of hip fracture) (Faulkner *et al,* 1993). It has been suggested that HAL is a marker for the ability of the femur or pelvis to absorb or avoid the impact of a fall (Faulkner, 1995).

There are important gender differences in both the shape of the proximal femur and pelvis including the pelvic brim (Beck *et al,* 1992; Wahner *et al,* 1994) which may influence bone strength or resistance to fracture. It is possible that one or more of these shape parameters interact with HAL, and explain the discrepant findings in relation to fracture risk in men and women.

In contrast to existing literature in women, results from this study show that hip axis length does not appear to be associated with the risk of hip fracture in Caucasian men and should not therefore be included in risk evaluation. There is therefore the need for caution in extrapolating the predictive risk of HAL observed in female Caucasians, to other population

groups. However, limitations of using a cross sectional study design in assessing predictive risk of the variable under study needs to be borne in mind.

4.3.5 Androgen

In this study there was also a clear and powerful association between the risk of fracture and male hormone levels. Hypogonadism was 5 times commoner in cases than controls and the risk of hip fracture associated with the presence of low free androgens was over 6 fold (OR 6.34). Because all blood samples were collected early in the morning after overnight fast, the criticism of previous studies (Stanley *et al,* 1991; Jackson *et al,* 1992; Boonen *et al,* 1997), that measurements may reflect diurnal variation, does not apply to this study.

Biochemical evidence of hypogonadism has been reported in upto 20% of men with vertebral fractures (Baillie *et al,* 1992) and upto 50% of men with hip fractures (Stanley *et al,* 1991; Jackson *et al,* 1992). However, these studies are limited by small numbers, heterogeneity in timing of sample collection (Jackson *et al,* 1992), selection of the control population (Stanley *et al,* 1991) and absence of BMD measurement (Stanley *et al,* 1991; Jackson *et al,* 1992; Abbasi *et al,* 1995). Assessment of hypogonadism based on chart reviews with their inherent problems of accuracy and completeness furthermore cast doubt on the results (Stanley *et al,* 1991; Abbasi *et al,* 1995). The recent case-control study reporting hypogonadism in men with an osteoporotic hip fracture (Boonen *et al,* 1997) is limited in controlling for the effects of trauma due to proximity in sample collection to the fracture event (18 hours) and its cross sectional design. Our observations of significantly reduced levels of androgens in the subjects immediately after the hip fracture which double at 6 months in the face of consistency of sampling time further support this criticism.

Another limitation of published case control studies is in determining with certainty whether the hypogonadism noted preceded the fracture or was secondary to fracture -induced debilitation. This methodological limitation has been overcome by prospective follow-up of the survivors which confirms significantly low male sex hormones in the fracture population compared to community controls even one year after the event. There was a marked rise in hormone levels between the baseline measurement and six months, which then stabilised on subsequent sampling. Although the continuing low hormone level may reflect a hitherto

unobserved long term sequelae of trauma, it seems reasonable to suggest that measurements six months after the fracture provide fair estimates of pre-fracture hormone status.

The mixed aetiologies of hypogonadism found in both groups are consistent with previously described primary testicular failure and alterations in hypothalamic-gonadotrophin function in ageing men. The only prospective population based cohort study failed to find a link between hypogonadism and male hip fractures (Nyquist *et al,* 1998) but its small size (10 hip fractures) means it was under-powered and must be interpreted with caution.

It is possible that low male hormones are a risk factor for hip fracture in men. Previous studies that have shown an association between low hormones and the risk of fracture have tended to assume that the association is mediated by BMD. This study was not designed to investigate that hypothesis. However, amongst controls this study was able to detect a positive association between androgen levels and bone density at all sites of the proximal femur (r_s=0.25, p<0.05) though not at the lumbar spine. In addition an inverse correlation was seen with bone markers (urinary deoxypyridinoline and osteocalcin r_s =-0.27 and -0.30 respectively). It may be conjectured that by regulating the rate of bone turnover androgens affect bone strength and quality and influence fracture risk.

This study, then, suggests that explanations for the association between hormone levels and the risk of fracture either lie with the proximal effects of low male hormones or with the effects of other factors which carry a risk of fracture and which lead to low hormone levels. The relatively high prevalence of "hypogonadotrophic hypogonadism" 6-12 months post-fracture which is often the result of long-standing ill-health (Nachtigall *et al,* 1997) may provide a significant clue. It may be reasonable to hypothesise therefore, that in the appropriate setting low testosterone is a surrogate marker of chronic ill health and may be used as a screening tool to predict the group "at risk".

Although this study has clearly demonstrated the powerful association between low androgens and male hip fracture the study has its limitations. This study suffered from the expected difficulty of recruiting healthy very elderly age-matched controls when studying a predominantly geriatric population/disease. This explains why earlier studies in men with hip fractures have not looked at the very elderly (90+ age group). To overcome this practical

problem different analytical approaches to address this issue are reported and it seems unlikely that the strong associations noted are substantially artefacts of age.

In common with other studies in literature addressing men with hip fractures this is a case control design and has inherent drawbacks. A major difficulty is getting good estimates of pre-fracture hormone status for cases - a problem that has not been addressed in previous studies. With the inherent limitations of a case control design, measurements at 6 months are our best possible estimates of the pre fracture androgen status of these individuals. It is still the case that a large prospective cohort study is needed to provide a definite account of the role of male sex hormones in bone health.

4.3.6 Oestrogen

In community controls, oestradiol levels exhibited good correlation with BMD (range r_s=0.25-0.43). Correlations were better with BMD at all sites of the proximal femur than the lumbar spine and stronger with free oestradiol than total oestradiol. Similar observations have been reported by previous researchers using total oestradiol (Foresta *et al,* 1984; Slemenda *et al,* 1997;Anderson *et al,* 1998) and oestrogen / SHBG ratio (Greendale *et al,* 1997; Khosla *et al,* 1998). Of the two sex hormones (androgen and oestrogen), results from this study suggest free oestradiol to be the more important sex steroid predicting BMD at all sites. This supports the observation of the only pre-existing cross sectional study involving 37 healthy men that found BMD at all sites correlating more closely with oestradiol than with testosterone (Anderson *et al,* 1997).

Levels of both total and free oestradiol were significantly elevated immediately after the fracture and returned to values comparable to controls at 6 months. After burn trauma, oestradiol levels in males are elevated, sometimes very much (Dolecek, 1989). It has been postulated that these elevated levels arise from adrenal precursors (Plymate *et al,* 1987) and promotes alteration of hypothalamic function. The latter results in markedly reduced secretion of bioactive LH and diminished Leydig cell function. Significant associations noted in this study between oestradiol and acute phase proteins (CRP r_s =0.23 and serum albumin r_s =-0.23) support the role of acute phase response to the marked endocrine changes noted after fracture in this study.

There is dearth of literature on the role of oestradiol in causation of an osteoporotic fracture in men. This study was not designed to answer this question. However, with this in mind and, after adjusting for changes in serum levels associated with acute phase response, low oestradiol and free oestradiol levels were found to be a risk factor for hip fracture in men (OR 0.98 and 0.34 respectively). The values for the latter did not reach statistical significance. Using similar case-control study design low oestradiol levels have been reported in men with vertebral fracture (Francis *et al,* 1989) but not hip fracture (Boonen *et al,* 1997). Discrepancy in results may be related to sample size of the populations under study and timing of samples in relation to the fracture event. It may also be conjectured that differences in the magnitude of stress accompanying hip fracture compared to vertebral fracture may have a bearing on the degree of alteration noted in serum oestradiol levels between the two fracture types. Prospective studies are needed to better delineate the true role of oestradiol in male osteoporosis.

4.3.7 Vitamin D

Immediately post fracture 20% of cases had undetectable vitamin D levels (<5nmol/l) and low vitamin D (<10nmol/l) was 10 times commoner in cases than controls. It is likely that other risk factors such as being single, living alone or in institutions and presence of co-morbid diseases reducing mobility and thereby outdoor activity contributed to these very low levels in this group of elderly men. Low vitamin D levels persisted 6 months post fracture confirming hypovitaminosis D as a risk factor for hip fracture in men (OR 10.2). Several recent reports of vitamin D levels in men with hip fracture have included small numbers (<43) (Boonen *et al,* 1997; Thieuband *et al,* 1997; Diamond *et al,* 1998); all suggest low vitamin D levels as a risk factor for hip fracture. The only randomised, placebo controlled trial of vitamin D supplementation in a significant number of men did not show any difference in incidence of hip or other fracture between the groups after a mean follow-up of 3.5 years (Lips *et al,* 1996). Critics suggest this may be due to the high mean diet calcium intake in both groups masking any significant differences.

Fourteen percent of elderly Caucasian men living in the community in Cornwall were also found to be deficient in vitamin D. It was most common amongst those in institutions or living alone at home and less ambulant. Similar results have been reported in recent years

from the continent - 14% in an adult urban French population (Chapuy *et al,* 1992) and 6% among Swiss adults (Burnand *et al,* 1992). The authors relate vitamin D levels to latitude of residence and hours of sunshine. In contrast, men in North America have been shown to have a very low prevalence of vitamin D deficiency (Gallagher *et al,* 1998). An explanation for this difference is better sunlight exposure coupled with supplementation of dairy produce in the USA. Results from this study in combination with those published earlier highlight the common problem of vitamin D deficiency with resultant sub-optimal calcium absorption in elderly men living in community. Simple measures to replenish the deficiency status in these men will go a long way in fracture prevention.

4.3.8 Bone Markers

Men with hip fracture exhibit an imbalance of bone turnover with depressed bone formation (low osteocalcin) and higher bone resorption (high urinary deoxypyridinoline). Bone turnover has been studied after hip fracture in females (Akesson *et al,* 1993) but not in men. Similar findings were noted and, the authors suggested that this uncoupling of bone turnover might be an important determinant of low bone mass that characterise patients with hip fracture.

Type of fracture does not seem to significantly alter the levels of bone markers. It has been proposed that intertrochanteric fractures are the consequence of more severe osteoporosis than cervical hip fractures. In this study, levels of bone markers were similar amongst patients with either fracture type.

It has been shown that elderly patients in the presence of co-morbid diseases and poor mobility exhibit increased bone resorption. Fracture patients were more disabled and had more co-morbidities than the controls. However, no significant differences were observed between the two groups.

A good correlation was seen between the bone markers amongst the controls; a finding supported by earlier publications (Gallagher *et al,* 1998; Kenny *et al,* 1998). The study also demonstrated a good correlation between age and osteocalcin. The effect of age on bone markers in men is still controversial. Some report a decrease (Wishart *et al,* 1995), some an increase (Orwoll *et al,* 1990) while others show no relationship of bone turnover with age

(Resch *et al,* 1994). Differences in study populations and the radioimmunoassays used may contribute to these differences.

This study failed to provide evidence to suggest that the rate of bone turnover determines BMD in elderly men. No correlation was seen between osteocalcin and BMD and only a weak correlation with urinary deoxypyridinoline. Results in literature are mixed. Most (Sherman *et al,* 1992; Krall *et al,* 1997; Kenny *et al,* 1998) but not all studies (Kelly *et al,* 1990; Wishart *et al,* 1995) reveal an inverse relationship between bone markers and BMD most consistently at the femur.

4.4 Outcome: Morbidity and Mortality

4.4.1 Morbidity

The 40 fracture cases that survived for 24 months had extensive morbidity and poor quality of life quantified using the SF-36. Twelve needed institutional care and only 11 could walk and 7 dress independently. Hip fracture subjects scored significantly lower than the controls in all domains of the SF-36 except pain. The mean physical component score was 38.9 (compared to 46 in controls). The health assessment score was 0.83 (compared to 0.27 in controls) on a scale of 0-3 with zero implying functional independence. Two retrospective reviews of medical records (Poor *et al,* 1995, Diamond *et al,* 1997) have reported poor functional outcomes after male hip fractures. One study of 131 males reported that at 12 months 29% survivors were bedfast or chair and bedridden and 45% needed institutional care (Poor *et al,* 1995). Another study of 51 males reported 50% were institutionalised and had significant (17%) post fracture functional decline (Diamond *et al,* 1997) by 12 months.

Pre-fracture the cases had poor overall health shown by low mean BMI, low SF-36 scores in most domains and frequent co-morbidities. The single report focusing exclusively on fracture risks in males (Poor *et al,* 1995) and more extensive studies in females (Cummings *et al,* 1995; Ensrud *et al,* 1997; Guo *et al,* 1998) underline the important links between ill health and hip fractures.

4.4.2 Mortality

Presence of hip fracture increased the risk of death 8 fold (Hazards ratio 8.1). Mortality was 60% at 2 years compared to 10% in the control population. Mortality rate was most marked in the first 3 months following fracture (25%), with rates declining subsequently. Residence in institutional care at the time of the fracture, poor functional status pre-fracture and presence of co-morbidity increased the risk of death.

The previously reported mortality, with 16-37% (Poor *et al,* 1995; Aharonoff *et al,* 1997) of cases dying after fracture, probably under estimated mortality by limiting period of follow-up, excluding the very elderly and high risk cases residing in institutions and dependant on basic activities of daily living. Most workers have found co-morbidities as risk factor for high mortality (Jencks *et al,* 1988; Myers *et al,* 1991; Poor *et al,* 1995; Nettleman *et al,* 1996, Stavrou *et al,* 1997, Aharonoff *et al,* 1997). It has been argued that the excess mortality noted in men may be related to co-morbid factors which both increase the risk of death and hip fracture (Poor *et al,* 1995). Cause of death was similar in the two groups: infections and heart disease being the commonest. These are similar to those reported by Poor and co-workers (1995). The only study addressing residence at the time of fracture as predictor of mortality (Poor *et al,* 1995) failed to show an association. The difference in observation may be the small number of deaths (n=21) in the study by Poor and that the data was collected from retrospective chart reviews. No data exist on the effect of pre-fracture health on mortality in men.

4.5 Size of the problem and recommendations for the future

Male hip fractures are a neglected and major health problem. Replicating the Cornish pattern throughout England and Wales gives 10,000 male hip fractures annually with 5800 deaths and 1200 cases needing long term care 2 years post fracture. In women hormonal risk factors related to menopause with resultant low BMD are dominant causes of osteoporotic fractures including hip fractures. This study confirms low BMD as an important risk factor for hip fracture in men as in women. However, in contrast to data in women, low androgen levels associated with male hip fractures may be related to chronic ill health and not only normal physiological ageing process. The substantial mortality and morbidity of male hip fracture together with the existence of several potentially reversible risk factors suggest

there is an urgent need to initiate simple preventative measures in males as well as females. The study identifies "high risk" individuals as single men, living alone or in care, with multiple diseases, a history of falls and low BMI. Preventive measures such as ensuring adequate calcium particularly during childhood, encouraging regular exercise throughout adult life particularly walking in the elderly; giving vitamin D supplements, preventing falls and importantly improving general health should all be beneficial in reducing the burden of this neglected problem to the NHS.

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Index

Appendix 1.1

PROTOCOL

TITLE

Impact and risk factors for hip fractures in men with special emphasis to bone density, biochemical and endocrine parameters.

HYPOTHESIS

Osteoporosis is a major risk factor for hip fractures in males leading to increased mortality and morbidity.

Male osteoporosis leading to hip fracture is commonly associated with hypogonadism.

The early detection and treatment of male hypogonadism may reduce the risk of osteoporosis and hip fractures.

RATIONALE

Osteoporosis in men is a neglected and important clinical and public health problem. Hip fractures represent the most serious complication of osteoporosis in terms of morbidity, mortality, disability and medical costs. Hip fractures are the commonest fractures of the elderly. The current costs for care of people with such fractures is estimated as £940M. In 1990, about 30% of 1.66 million hip fractures worldwide occurred in men. The respective risk at 50, 70, and 90 years of age is 2.4, 3.8, and 7.9% in men; and 9,11.7, and 17.5% in women. Hip fractures in men account for one third of all hip fractures and have a higher mortality than in women. By the ninth decade of life, 4% of men will have sustained a forearm fracture, 7% a vertebral fracture and 5% a femoral neck fracture. The age specific incidence of hip fractures is increasing. Although the risk of hip fractures in men and its associated morbidity, mortality and cost is substantial, very few studies have been directed in this direction. Some of the recognised risk factors for hip fractures in men are pre-admission ambulatory problems, confusion, heavy alcohol intake and low body mass. It is not known whether the risk factors in men differ from those in women or whether there is a sex variation in the relative importance / contribution of these risk factors.

Bone is lost with advancing age in men as in women. Bone mass correlates with strength and this bone loss leads to an increased incidence of osteoporotic fractures of the forearm, vertebral body and femoral neck. However, the relative contribution of low bone mass, that is osteoporosis, to fractures in men has not been fully established. Studies on osteoporosis have focussed largely on the enormity of the problem in women. More data is therefore needed on contribution of bone density to hip fractures in men.

Sex hormone deficiency is a well-documented and important cause of bone loss in women and men. Men have a greater bone mass at all stages presumably because of a higher peak bone mass at skeletal maturity, and absence of a distinct phase of accelerated bone loss at mid life. Although in women, menopause is a dominant contributory factor to the latter, it does not exclude the gradual bone loss from midlife in men to be associated with hormonal factors. It is known that there is an age associated decline of sex hormones levels in men but its contribution, to risk of osteoporosis and or fractures in men has not been well established. Little data exists correlating sex hormone levels to bone mineral density and fracture risk in men.

It is with this idea, that we plan to look into the descriptive epidemiology of hip fractures in men aged 50 years or more with special emphasis to assess the remedial causes that may be targets for preventive strategies in future.

OBJECTIVES

1. To establish the descriptive epidemiology encompassing risk factors and outcome of hip fractures in men aged 50 years and above in Cornwall.
2. To find a correlation, if any, of bone mineral density and sex hormone levels to risk of fracture, in men.

STUDY DESIGN

A prospective, case control study of men aged 50 years or more, residents of Cornwall, presenting to the Royal Cornwall Hospital with hip fracture in a one year duration. All cases will undergo detailed evaluation for possible risk factors for the fracture, bone mineral density, biochemical and endocrine studies and functional assessment.

Equal number of healthy age matched men would be analysed for serum testosterone levels to determine the prevalence of hypogonadism in the general population, as this may be an important treatable cause of osteoporosis in this population.

Functional assessment, outcome and development of any new fracture in all patients will be analysed at baseline and every 6 months for 2 years.

INCLUSION CRITERIA

Men aged 50 years or more, resident of Cornwall, consecutively admitted with a hip fracture following fall from standing height or less.

EXCLUSION CRITERIA

1. Men with hip fracture NOT residents of Cornwall.
2. Hip fractures due to "major trauma" will be included when counting for insight into the epidemiology of the condition, but excluded from BMD, biochemical and endocrine assessment.

ASSESSMENT

At First Visit

Clinical: "risk factor" questionnaire

Functional: "functional assessment" questionnaire- includes SF 36 plus disease specific questions of the MEDOS questionnaire.

Radiological: Xray thoraco-lumbar spine (lateral view)
Bone mineral density (lumbar spine and femoral neck); in patients with bilateral hip fracture/ replacement and/or multiple spinal fractures making analysis at 2 sites technically difficult forearm densitometry will be added.
Hip axis length measurement

Laboratory: Full blood count
Routine biochemistry
Thyroid function tests
Cholesterol and triglycerides
Serum/urine electrophoresis
Parathyroid, 25 OH Vit D
S Prolactin,
S Cortisol
S Testosterone, SHBG, FSH, LH
Prostate specific antigen
S Osteocalcin, Bone Alk Phos
24 hour urinary calcium
Urinary Calcium/creatinine ratio
Urinary crosslinks
? Cytokines IL1, IL6

At follow up visits

Postal/ Clinical review to assess outcome and to identify any further fracture.

Functional assessment questionnaire every 6 months

BMD every 6 months in patients requiring active intervention

Serum chemistry individualised to each patient depending on his risk factor

S Testosterone, lipid profile and PSA every 6 month of patients on hormone replacement.

TREATMENT

All patients will be advised to lead an active healthy lifestyle, spend time walking out of doors for at least half an hour each day and ensure adequate Calcium and Vitamin D by diet or supplements. In men, with low androgen levels testosterone replacement therapy will be administered. Blood for PSA, lipid profile, FBC and androgen levels will be monitored every 6 months and repeat BMD measurements carried out at 18 months.

Studies of incidence rates of hip fracture in men by decade

Country	Race	Year of study	50-59	60-69	70-79	80+	Reference
Norway	White	1978-79	54	226	523	1598	Falch *et al*
	White	1983-84	67	346	867	3234	Finsen & Benum *et al*
Sweden	White	1972-81	78	182	478	1419	Hedlund *et al*
Finland	White	1968	24	54	154	559	Alhava *et al*
Denmark	White	1973-79	48	129	307	1119	Frandsen *et al*
UK	White	1973-77	20	51	140	548	Baker *et al*
USA	White	1965-74	37	92	192	1281	Gallagher *et al*
	White	1980	31	104	192	1641	Bauer *et al*
	White	1983-84	37	90	334	1209	Silverman *et al*
	Black	1983-84	46	84	190	816	Silverman *et al*
	Asian	1983-84	16	49	155	739	Silverman *et al*
	Hispanics	1983-84	15	34	150	600	Silverman *et al*
	Hispanics	1980	18	31	214	816	Bauer *et al*
Johannesburg	Black	1950-64	20	30	40	170	Solomon *et al*
Hong Kong	Asian	1965-67	17	71	224	321	Chalmers *et al*
	Asian	1985	28	54	339	1156	Lau *et al*
New Zealand	White	1973-76	27	51	186	862	Stott *et al*
Singapore	Asian	1955-62	20	70	210	350	Wong *et al*

RISK FACTORS FOR HIP FRACTURE (NON BMD)

Variable	Grisso JA *JBMR 91*	Hemenway D *Am J Pub Health 94 Health Professionals FU study*	Poor G *JBMR 95*	Nguyen TV *Am J Epid 96 DUBBO*	Grisso JA 9 *Am J Epid Hip Fracture Study Group*	Mussolino ME *JBMR 98 NHANES Epidemiologic FU study*	Langlois JA *Arch Int Med 98 EPESE study*
No (men)	54; > =35	49,895; 40-75y	232; > =35	820; >=60	356 fracture/402 con; age >=45	2879; >=45	2413; > =65
Study Design	CC; chart reviews	longitud;2/4/6y FU	Nested CC; info fm med notes	longitud; 5yFU; M+F	CC;	longitud; 22yFU	longitud; 8yFU
No. hip fracture	54	67	232	All 166. hip 31	356	21	72
Maternal H/o fracture	NT	NT	NT	NT	NT	NT	NT
Previous H/O fracture	NT	NT	RF; all fracture OR 3.0	RF (after adj for FN BMD)	NT	NS	NT
Age	NT	age >65y is a RF	NT	RF	NT	RF	RF
BMI	RF: low BMI	no relationship found	RF	NT	RF; OR 3.8	NT	RF

Variable	Grisso JA *JBMR 91*	Hemenway D *Am J Pub Health 94 Health Professionals FU study*	Poor G *JBMR 95*	Nguyen TV *Am J Epid 96 DUBBO*	Grisso JA 9 *Am J Epid Hip Fracture Study Group*	Mussolino ME *JBMR 98* *NHANES Epidemiologic FU study*	Langlois JA *Arch Int Med 98 EPESE study*
Wt	not mentn	not mentn	RF	RF	NT	NS	>10%loss-RF (RR1.8); >10% gain protectn (RR 0.4)
Ht	not mentn	RF-height>6ft	RF; taller	shorter ht RFfor fracture	RF; /6cm OR 1.2	NS	not mention
Smoking	NS	no relationship found; <3% sample smoked	NS	dec BMD; but NS for fracture	current>=1pack/d-inc: OR 3.2; pipes-inc: OR 2.5; past-inc: OR 1.4	current-inc; but NS	NS
Alcohol	RF"-heavy" use	no relationship found; only 4% heavy drinkers	NS	less BMD loss over 2yr	current/past-not RF	any ROH-not RF	NS
Calcium	NT	NT	NT	sig inc FN/LS BMD; not RF for fracture	NT	dec risk fracture but NS	
Exercise	NT	NT	inactivity RF; OR3.4	high-protective for fracture	>=7h/wk dec risk fracture; OR 2.5	low-inc risk fracture but NS	
Drugs	NS; sedatives, psychotropic	NT	NS: CS, thiazides, anticonvul	NT	thiazides-no ass; psychotropics-inc: OR 2.2 cimetidine-inc: OR 2.5	NT	thiazides-NS

Variable	Grisso JA *JBMR 91*	Hemenway D *Am J Pub Health 94 Health Professionals FU study*	Poor G *JBMR 95*	Nguyen TV *Am J Epid 96 DUBBO*	Grisso JA 9 *Am J Epid Hip Fracture Study Group*	Mussolino ME *JBMR 98* *NHANES Epidemiologic FU study*	Langlois JA *Arch Int Med 98 EPESE study*
Co-morbid diseases	RF: stroke, parkinson	NT	RF: hemiplegia OR 2.6; Parkins OR 8.0; dementia OR 5.3; blindness OR5.5; vertigo OR 6.0; anemia OR 2.6; thyroidectomy OR5; gastric surg OR2.6	NT	stroke-OR 4.2; parkinsons OR 7.9; >= 2 chr dis OR 2.5	RF: >= 2 chr dis- RR 1.95	NS
ADL	RF: use of aids	NT	chr bronchitis OR 2.3 RF- use of aids cane/walker OR1.7		LL dysfn-OR4.5; use of aids OR 3.7; diff with >= 1ADL OR 4.2		RF not sig
Others	Low mental status-confusion but NS as RF	NT		RF: Previous falls(1yr); Higher body sway; Low quads strength; BMD		Phalangeal BMD RA=RF	low mental status-RF

BMD DETERMINANTS IN HEALTHY MEN

Variables	**Mazes RB** *JBMR 90*	**Hannan MT** *JBMR 92* *Framingham*	**Felson DT** *JBMR 93* *Framingham*	**Edelstein SL** *Am J Epid 93* *Rancho-Bernado*	**Burger H** *Bone & Min 94* *Rotterdam*	**Nguyen TV** *JBMR 94* *Dubbo*	**Slemenda CW** *An Int Med 92* *Twin*	**Wishart JM** *Clin Endo 95*
No	315 (Lspine): 282 (Femur)	366 +562 fem	366 +562 fem	597 +895 fem	678 +1084 fem	790 +1080 fem	80 pairs (38MZ; 42 DZ)	147
Age grp	20-89	Mean 76	Mean 76	55-84; av 72	> 55	> =60	Av 47 to av 63	20-83; av 48
BMD method	DPA	DPA; SPA radius	DPA; SPA radius	DXA; SPA radius	DXA	DXA	SPA	SPA/DXA
Sites	LS/Femur	Femur / radius	LS/ Femur/radius	LS/Femur/radius	LS/ Fem	LS/Femur	Radius; 0&16y	Radius, LS/Fem
Age	No sig change in spine/troc BMD ; Correl with FN/Ward BMD – 0.58/0.69; annual rate of loss 0.5-0.7%/yr	Neg correl with BMD Linear decline of fem & prox radius BMD with age; not ultradistal radius	refer JBMR 92; Hannan et al	NT	Non sig increase in LS BMD with age; Fem sig dec with age at all sites	Decline of 10% in FN BMD bet age 60 &80; no change in LS Independent predictor of BMD	NT: pairs foll for 16 yrs	Sig deficit by age 50 only in Wards; Fell sig after age 50 at all sites except LS/ troch;
BMI	NT	NT	Sig	Sig with LS/F not Radius	Sig correl with BMD all sites	Correl with BMD	No correl with rate of bone loss	
Ht	NT	NT	NT	NS	NT	+ correl (0.3-0.5)	Current BMC +corr ; bone loss not correl	
Waist –hip ratio		NT		NS	NT	NT		
Hip girth		NT		NS		NT		
Lean mass		NT		Sig ; not radius		NT		
Fat mass		NT		Sig ; not radius		NT		

Variables	Mazes RB *JBMR 90*	Hannan MT *JBMR 92* *Framingham*	Felson DT *JBMR 93* *Framingham*	Edelstein SL *Am J Epid 93* *Rancho-Bernado*	Burger H *Bone & Min 94* *Rotterdam*	Nguyen TV *JBMR 94* *Dubbo*	Slemenda CW *An Int Med 92* *Twin*	Wishart JM *Clin Endo 95*
Alcohol		NT				Sig predictor of BMD; +correl NS	Sig –ve correl with amount of bone loss in 16y	No relation
Smoking		NT				Sig predictor; LSBMD: ex =never smoker; Fem: current<ex<never	Sig -ve correl with amount of bone loss in 16y	No correl
Diet Ca		NT				Sig predictor at all sites	No correl	No correl
Quads strength		NT				Ass with Wards / troch independent of wt		
Physical activity							-ve correl with bone loss	
Genetics							Similar rates of bone loss commonly in MZ due to shared environ	
Bone markers-form & resorp								No sig correl with any marker

BMD AS RISK FACTOR FOR HIP FRACTURE IN MEN

Variables	Karlsson MK *Bone 93*	Greenspan SL *Am J Med 98*	Gardsell P *Bone 90*	Nguyen TV *Am J Epidemiol 96*	Boonen S *JBMR 97*	Nyquist F *Bone 98*	Mussolino ME *JBMR 98*
Design	CC	prospective CC - all NH residents with h/o fall	Prospective	prospective pop DUBBO	CC; cross sectional	prospective pop based	prosp, epidemiol - NHANES
No. of cases	93 fracture; 195 C age >=50y	total 132; age >=65yrs fall + fracture =case=32, fall no fracture=control= 100	654	820 men age > 60y; foll 2y	40 fracture; 40 controls	242 men age 50-80 y; foll 7 y	2879 men age 45-74 yrs; follow up 22 yrs
No. of hip fracture	men 26 fem 67; all 93	men 7 fem 25; all 32		31, all 166	40 fracture	9 hip, all 321	71 hip
BMD method	DEXA LS/ hip	DEXA hip only	SPA at forearm	DEXA LS/hip	DEXA hip only	SPA forearm	phalangeal; n=1437
Duration between fracture & BMD	10days	1 week	over 11yrs	DXA at 0 (n=752) and at 2 yrs (n=442)	1 week	over foll of 7 years	Fractures over followup of 22 yrs
BMD	sig low spine /hip in fracture patient.	sig lower at hip in those who fell & fracture Vs no fracture	lowest quintile 6-13x risk	baseline BMD sig lower at hip (12%) / spine (17%) in fracture Vs non fracture	sig lower at fem	sig low-RR 3.88 of hip fracture for 1 SD decrease BMD	70% increase in risk of hip fracture with 1SD dec in BMD
Age	NT	with fracture sig older Vs no fracture		Fracture pt sig older than non fracture subject			
BMI	sig low	not associated		Fracture pt shorter by 4cm (sig)			

Variables	Karlsson MK *Bone 93*	Greenspan SL *Am J Med 98*	Gardsell P *Bone 90*	Nguyen TV *Am J Epidemiol 96*	Boonen S *JBMR 97*	Nyquist F *Bone 98*	Mussolino ME *JBMR 98*
Weight	sig low	NS		10% lower wt in fracture pts (sig)			wt loss >10% ass with 2fold increase in hip fracture risk
Type of fracture	no sig diff in BMD cx/troc	NT					
Living status	sig lower BMD in those living alone	NT					
Smoking	no diff in BMD smokers vs non smokers	NT					
Aids	no sig diff in BMD	impaired mobility sig in those with fracture Vs no fracture					
Falling indoors/ outdoors	no sig diff in BMD	NT					
Vision	no sig diff in BMD	NT					
Previous fracture	no sig diff in BMD	NT		sig RF for any fracture (within 5yrs)			
Falling tendency	no sig diff in BMD	falls to side sig more in fracture cases		falls within 12 M sig RF for fracture: higher body sway sig RF for fracture.			
Mental status	NT	sig impaired mental status in fracture cases					

HIP AXIS LENGTH

Author / Journal	Study design	No. case/control	Aim	Measurements	Comments	Results
Rev Rhem Engl Ed 97			Establish normal ranges; check feasibility of HAL as a measure in clinical practice	HAL in 50 women twice (short term) and in 60 women every 6M x5times(long term) HAL Rt vs Lt Single vs Fan beam Ht, Wt, FN BMD	All women Type of Xray beam inportant fan / pencil	Reproducibility of HAL measure by DXA is 1.67% (short-term) and 1.5% (long term) HAL Rt no significantly different from Lt HAL correlates to Ht, NOT with age/FNBMD Sig diff single beam VS fan beam
Spector T JBMR Apr 96		500 female twins-128 identical; 122 non identical	Determne genetic basis of BMD, HAL and US calcaneum	BMD HAL US calcaneum	Twins Postmen women	BMD strongest genetic component-estimates of heretability 0.46-0.84 HAL , Vel of sound had major genetic component-estimates 0.62 and 0.61; independant of BMD Broadband US moderate genetic comp-estimate 0.53 All 3 measures independently heritable and independently risk factors Hence, different genetic factors acting on dimension/ structure/ density of bone explain importance of family history as risk factor for fracture
Hayes JG, Nguyen TV *JBMR 95*			VDR and HAL			Association between VDR alleles and HAL
OI 96		189 female dizygous twin pairs	Role of VDR on other parameters (HAL & US calcaneum) ass with fracture risk	US calcaneum HAL VDR genes	Twins	No association between VDR polymorph and HAL or US calcaneum search for alternative genes influencing bone fragility to continue

Author / Journal	Study design	No. case/control	Aim	Measurements	Comments	Results
OI 97		n=225 women Chinese, Indians, Polyneasian	Assess femoral neck and HAL in 3 ethnic groups and compare it to Europeans	HAL via DXA Ht, Wt	Women only	Shorter fem necks and HAL common in Asians cf Europeans However, Polynesians have longer fem necks and HAL BUT LOWER incidence of hip fracture cf Europe - not explicable in terms of FN length Poly &Europ taller than Asian, Chinese Poly heaviest; Chinese lightest
JBJS Sep 91			Assess racial diff in femoral dimensions			
JBMR Nov 97	Case-control case =EPIDOS	n=167 controls n=66 fracture (42Cx, 24 troch) all F	Measure HAL & BMD by DXA to determine as predictors of type of fracture.	HAL, BMD	Women only	HAL in Cx frcature significantly longer than controls (94.2VS 92.3); HAL in trochanteric fracture not different than controls FN diameter not a predictor of fracture.
Center JR, Nguyen TV, Sambrook PN (Australia) *OI 98*	Case-control populatiin based (DUBBO)	123=female (23 fracture, 100C) 137=men(13 fracture, 65+59C)	Examine association between FNAL and hip fracture	FN BMD by Lunar FNAL	Men & women	FNAL has limited utility in predicting hip fracture FNAL correlated sig to current Ht & peak Ht FNAL in fracture patients NOT different from controls- both men and women Peak Ht in females and Ht loss in men risk factors for hip fracture NOT FNAL
Karlsson KM Malmo, Sweden *Bone Apr 96*	Retrospective study 125 consecutive hip fracture cases 192 controls	Cases - 33 men and 92 women controls - 92 males and 100 females		HAL by Lunar 2 weeks after fracture Width fem neck Fem shaft-neck shaft angle	Men & women HAL measured using ruler not automated = FNAL	male hip fracture cases had shorter HAL(FNAL) than controls on Xray.; by DXA no sig diff in HAL(FNAL) between fracture and controls
Reid IR, Chin Kr *BMJ 1994*					Women	HAL increased by 1SD from 1950-1990 Probably explains increase in hip fracture incidence

Author / Journal	Study design	No. case/control	Aim	Measurements	Comments	Results
Duthie RA (Aberdeen0 *BMJ 98*	71 (28 women) died 1900-1920; 49 (27 women) died 1980	120 cadaveric femurs	Osteometric study to confirm increase in FNAL over decades	Femoral length, fem head diam, neck width, neck length using osteometric board	Cadaveric femurs men and women	FNAL, fem length, neck width, head diameter has sig increased over the years No sig change in fem neck anteversion
Faulkner KG San Francisco (SOF Res Gp) *JBMR 93*						
Faulkner KG San Francisco (SOF Res Gp) *Calcif tissue Int 1995*						
Peacock M *OI 1995*						
Nakamura T *JBMR 1993*						
Boonen s *JBMR 1995*						
Cummings SR (SOF Res Gp) *OI 1994*	Study of Osteoporotic fracture cohort	135 caucasians 74 Asians 50 Blacks	shorter HAL can account for less fracture risk in Asians and blacks	HAL	Women only-Caucasian Vs Black & Asians	HAL of Asian and Black women significantly shorter than whites HAL may account for lower fracture risk in these races
Theobald TM San Francisco (SOF Res Gp) *OI 98*	Study of Osteoporotic fracture cohort	132 African-Am women 43 Nigerain women 165 Caucasian women	Examine racial diff in hip geometry to explain difference in fracture rate	Cortical thickness Inter trochanteric bone width HAL BMD	Women-Caucasian VS Africans	Cortical thickness greater in African Vs Caucasians HAL & bone width smaller in African Vs Caucasian Above racial diff contribute to 25% decrease risk of fracture in blacks

TESTOSTERONE AND BMD IN HEALTHY / HYPOGONAL MEN

Author/ Journal	Study design	No. case/control	No. of fracture	Measurements	Comments	Results
Rudman D et al Wisconsin, US *Clin Endocri 94*	Cross sectional design -healthy men only; age 58-95 yrs	I: 49 men free living II: 49 men in institutions	compare healthy men free living vs living in care	Ht, wt, BMI, mobility score testsoetrone,IGF-1 BMD, TBBMC, LBM	DEXA L Spine and hip Early morn samples	BMD, TBBMC, LBM sig low in free vs in -care men. IGF1, testosterone significantly low in in care men. In gpI: testosterone most important predictor of BMD, TBBMC, wt; in multivariate analysis age etc had no significant predictive ability after testosterone entered into equation; age predicted LBM/ht ratio In contrast in gpII: age, wt, mobility score significant independent predictor of BMD, TBBMC, LBM Testosterone significant correlation to FN BMD but not in multivariate analysis ie age and immobility more powerful risk factors for low BMD than low testosterone
Foresta C et al Italy *Hormone Res 84*	Cross sectional design- healthy males	60-90 yrs; n=30 20-40 yrs; n=20	Compare young vs older healthy men	BMC II phalynx (% cortical area) testos, androstenedione, estrone, estradiol	% cortical area (PCA) measured using BMC at II phalynx of lt hand index finger Blood early morn by RIA	BMC sig lower in elders cf young testosterone, estradiol, estrone not significantly different, androstenedione significantly lower elders vs young + correl bet PCA and testos, andros, estrone no correl bet age and PCA
Ongphiphadh anakul B et al Bankok *Clin Endo 95*	Cross sectional design- healthy men	20-80 yrs age; n=90	In healthy men study effect of age on HPG axis, BMD & body composition	BMD- Lspine, Femur testosterone, free testosterone, LH, FSH Ht, wt, diet Ca	DXA Lunar early morn sample	Age/ wt no correlation; age/ht -ve correlation; Ca intake/BMD no correlation Age/ BMD (LS, FN, Ward) -ve correlation; age/ TBBMC no correlation; age/ % body fat+ve correlation; age/ % non fat soft tissue -ve correlation. Age/ free testcosterone -ve correlation; testosterone no significant change with age; LH/ FSH increase sig with age-+ve correlation Free TT sig +ve correlation with LS, FN, ward BMD; still significant after adj to age Free TT, testosterone.+ve correlation to body fat; free TT, testosterone -ve correlation to LBM, both true after adj for age On regression-age, free TT, LBM imp determinants of FN, ward BMD

Author/ Journal	Study design	No. case/control	No. of fracture	Measurements	Comments	Results
Drinka PJ Wisconson, US *Calcif Tissue Int 93*	Cross sectional design subjects with known risk factors/diseases included ie ambulatory elderly men with and without disease	Age >=65 yrs; n=112 (53 healthy) 35/122 had FU tests at 4yr	Study association of free TT & BMD separate from age	SPA radius, ultra distal radius, DPA for Lspine, femur DXA at FU 4yrs later	Population mixed-healthy and diseased BMD measured by diff methods at diff sites at both visits-SPA, DPA DXA Numbers in tables do not match to description	Did not detect sig association between freeTT and BMD
Finkelstein JS et al Massachusetts *J of Clin Endo & Metab 95*	Longitudinal study over 2 yrs of BMD and OC/UHPr in men with h/o delayed puberty cf normal men	23 men with h/o delayed puberty; age 26-31 yrs reassessed in 2 yrs control n=24; age 23-40	effect on peak BMD in men with h/o delayed puberty	23 men studied to assess radial/spinal BMD; OC & UHPr compared to 23 controls 18/23 reassessed in 2 yrs; femoral BMD added	BMD radius-SPA BMD spine DXA BMD femur (only at 2 yr) DXA samples AM	Mean spinal and radial BMD at baseline sig lower in cases vs healthy normal men mean BMD unchanged at radius and Lspine in 2 yrs Mean BMD at femur sig lower than normal men OC and UHPr were normal- hence bone turnover is normal in these men men with h/o delayed puberty have permanent decreased peak BMD with no change over 2yrs cf normal men
Francis R et al Leeds, UK *Bone 86*	Interventional study 9/13 hypogon treated with sustanon	Heterogenous group of hypogonadal men age 31-79 n=13 7 had vertebral fracture, 6 had no fracture	Pathogen and pattern of bone loss in hypogo men effects of of TRT compare hypogonadal with vertebral fracture to no fracture	Clinical details testos, E2, LH, FSH, 25 OHD, 1,25 OHD, PTH, bone profile, Urine CaCr, U hydroxy proline, Xray femur, Lspine, hand Iliac bone biopsy	Metacarpal cortical area/total area; femoral cortical area/total area; Singh index	Untreated: low testos, raised LH?FSH, variable E2 Low MCA/TA, FCA/TA, low Singh index low bone vol, increased resorption, low appositional rate, low trabecular number radiocalcium low with low 1,25 OHD but normal 25OHD; Ca, Po4 normal strong correl bet radiocalcium and 1,25OHD Urine HPr/Cr correl with Alk Phos and UCa/Cr men with fracture sig lower MCA/TA, Singh index, bone vol, trabecular number, 1,25OHD cf non # grp PTH correl with Urine Hpr/Cr Treated: increased testos and E2, fall in FSH/LH, Increased 1,25OHD and radiocalcium abs Po4 dec, UCaCr dec, no change in urineHPr/Cr Osteoid surface inc, dec appositional rate

Author/ Journal	Study design	No. case/control	No. of fracture	Measurements	Comments	Results
Arisaka O et al, Tokyo, Japan ***Metabolism 95***	Longitudinal, intervention study over 2yrs Initial randomized open phase for 1yr with two parallel gps: 6 pt on TRT, 6 not on TRT Next, 1yr open phase with all on TRT	Age 15-21 yrs n=12 all hypogonadal control n=117 age 12-30yrs to compare baseline BMD	Effects of TRT on BMD & bone metab in pubertal hypogon men compare BMD hypogon vs controls	TRT for 2 yrs BMD 0, 12, 24 using SPA OC, 25 OH, 1,25 OH, IGF1, PTH at 0, 12, 24	BMD using I125 SPA radius AM samples	BMD significantly low in all the 12 hypogonadal men cf normal controls (n=117 aged12-30) BMD significantly increased on TRT when gp entered into TRT arm Osteocalcin increased significantly when TRT started PTH, 25 OHD, 1,25 OHD no significant change with TRT PTH - VitD axis normal in hypogonadal men
Anderson F et al Newcastle upon Tyne UK ***Bone 96***	Open prospective therapeutic trial	Eugonadal men with established OP (vertebral fracture) n=23 age 34-73 yrs	Effect of TRT on BMD over 6M	Men with vertebral fracture and OP TRT q 2wk x 6M BMD 0, 6 DXA testos, FAI, Urine Hpr, routines	Also assessed health, psychological effects, Side effects etc	5% increase in Lspine BMD in 6M; no significant change at femur Ca, Po4 unchanged Uca, Hpr non sig decrease No change in 25OHD

TESTOSTERONE AND HIP FRACTURE

Author/ Journal	Study design	No. case/control	No. of fracture	Measurements	Comments	Results
Nyquist F Sweden ***Bone 98***	Prospective population based cohort	242 age 50-80 patients with fracture included	31(hip 9) over 7yrs Aim: whether BMD alone or with other variables eg testosterone can predict OP fracture	Forearm BMD. SPA:Testosterone, shbg,skin fold thickness	Blood samples before noon; not AM Pt with h/o fracture not excluded n=57 Total no of hip fracture only10	1SD decrease in forearm BMD RR of OP fracture 1.75 95%CI (1.08-2.83); RR hip fracture 3.88 95%CI (1.3-11.57) Similar RR for fracture with skin fold thickness Testos &SHBG did not enhance fracture prediction No correl of testos with forearm BMD No difference in testosterone between patients who develop fracture and those without over the 7 yrs
Jackson JA Texas ***Am J Med Sci 92***	Case-control	n=28 fractures; n=28 community controls (matched 5yrs)	n=28 (17 fractures prospective over 10mth + 11 of 27 fractures retrospective over preceeding 25 months	Clinical, comorbid cond, drugs, Routines, Testos, FreeTT, LH No BMD	Pooled blood samples q 20min between 5-9AM In prospective cohort samples pre & 48h postop. OR for hip fracture calculated	Testosterone. FreeTT significantly lower in fracture group vs control group. Primary vs Secondary hypogonadism ratio 2:1 in fracture group; 8:1 controls Odds of fracture 5 times in hypogonadal men vs eugonadal men. Ca, Alb significantly lower in fractue group 25 OH VitD significantly lower in fracture group Gonadal deficiency risk factor for fracture.
Stanley HL Virginia ***J Am Geriatr Soc 91***	Case-control selected control population. time since fracture not mentioned	n=19 fractures, n=65controls	Over a 5day pd all male NH residents 65+ (n=84) eligible. After chart reviews hip fractures n=19=cases; rest =65=controls	Chart reviews: H/o MTHF, comorbid dis, drugs Single random freeTT of 17 fractures and 61 controls No BMD	Historical data from chart reviews. Single random sample before noon. OR for MTHF in hypogonadal vs eugonadal calculated. GOOD DISCUSSION	FreeTT lower in patients with fractures vs controls 10/17 (58.8%) with fracture hypogonadal vs 11/61 (18%) controls hypogonadal Odds of fracture 4.6 times in hypogonadal vs eugonadal. This association not confounded by age, race, ROH, cig, medical disease, drugs Hypogonadal men increased risk of MTHF

Author/ Journal	Study design	No. case/control	No. of fracture	Measurements	Comments	Results
Abbasi AA, Milwauke, USA ***Am J Med Sci 95***	Observational (chart reviews)	In a NH 31 hip fracture survivors (29M=2F)- Fracture 6M - 8yrs prior to study !	GrpI: Healthy young n=25 GrpII: Healthy old n=78 GrpIII: post hip fracture n=29M mean age=78y	Chart reviews like an audit: wt, smoking, ROH, Ca VitD, mobility, drugs, exercise, hypogon BMD in only 10 of 29 fracture + all GrpI &II	Fracture 6m to 8 yrs prior to study. Only 10 of 29 fracture had BMD BMD only of femur Only post fracture survivors -bias	Poor management of hip fracture patients in NH No mention of osteoporosis / risk factors in hip fracture survivors No intervention to improve bone health/ physical fitness. Most on suboptimal Ca 66% hypogonadal, 36%current smokers, 55% immobile. 65% on drugs causing bone loss
Boonen S Leuven, Belgium ***JBMR Dec97***	Case-control, cross sectional	n=40 #, n=40 CC	n=40	Testosterone, 25 OHD, 1,25 OHD, PTH, E2, OC, deoxy pyridinoline BMD-femur DXA; not spine	Cross sectional design Single sample close to fracture (18hrs)	Androgen def- total, free TT significantly lower cf controls; DHEAS significantly lower cf controls Low 25, 1,25 Vit D cf controls Low BMI, wt, alb cf controls PTH/ LH significantly increased cf controls E2 / SHBG not significantly diff Urinary pyr & deoxy pyr significantly increased Femoral BMD significantly low

OESTRADIOL IN MEN

	Greendale GS ***JBMR*** *1997*	**Khosla S** ***J Clin Endo & Metab*** *1998*	**Gillberg P** ***Calcif Tissue*** *1999*
Study design	The Rancho Bernado Study 534 M & 457 F (50-89yrs)	Population based 346 men (23-90yrs)	Case-control 12 men with idiopathic OP, 12 matched controls (27-55 yrs)
Effect of age	NT	Oestradiol and bioavailable E2 decreased with age	Lower oestradiol, E2/SHBG, FAI in cases cf controls
Relation with BMD	+ve correl with BMD at all sites Bioavailable better correlated than total E2	Bio E2 +ve correlation with total body, FNeck, distal radius Independent predictor of BMD	Sig correl of oestradiol/SHBG ratio to FN BMD in cases NOT controls 76% variation in FN BMD explained by E2/SHBG ratio and age
Relation with bone markers	NT	-ve correl with urine NTx	
Conclusion	Bioavailable estrogen most strongly associated with BMD Bioavail testos correl to BMD in men No association bet total testo, DHEAS and BMD	Bioavail E levels decline sig with age and is an independent predictors of BMD	Despite values in the normal range, men with idiopathic OP had sig lower oestradiol, E2/SHBG, FAI cf controls +ve correl between E2/SHBG and FN BMD in men with OP

BONE MARKERS IN HEALTH AND AS PREDICTORS OF HIP FRACTURE

	Resch H	Epstein H	Worsfield M	Catherwood BD	Sherman SS	Paulus LA van Daele	Garnero P
Variables	*Miner Elect Metab 94*	*Clin Chim Acta 88*	*Clin Chim Acta 88*	*Bone 85*	*JBMR 92*	*BMJ 96 Rotterdam*	*JBMR 96 EPIDOS*
Subjects	Healthy	Healthy	Healthy	Healthy	Healthy	Fracture: 17 hip	Fracture:109 hip
No	155: 64 M, 91 F				191 M; 120F	10,275F; >55yrs	7598 F; >75yrs
BAlk Phos	NS diff >/< 50yrs age					NT	Not RF for fracture
OC	NS diff >/< 50yrs age	Increase with age	Decline with age	No change with age	no correl with age/ BMD except in old women & young men	NT	Not RF for fracture
U NTX					NT	NT	Not RF for fracture
U CTX					NT	NT	Sig independent RF for Fracture; OR 1.3 / 1SD inc in CTX
U Free DPyr					NT	by ELISA sig RF for hip fracture independent of BMD	Sig independent RF for fracture; OR 1.4 / 1SD inc in free Dpyr
U Ca/Cr					no correl with age/ BMD any site, F/M		
mPTH	NS diff >/< 50yrs age				NT	NT	NT

	Resch H	Epstein H	Worsfield M	Catherwood BD	Sherman SS	Paulus LA van Daele	Garnero P
Variables	***Miner Elect Metab 94***	***Clin Chim Acta 88***	***Clin Chim Acta 88***	***Bone 85***	***JBMR 92***	***BMJ 96 Rotterdam***	***JBMR 96 EPIDOS***
25 OHD	NS diff >/< 50yrs age				+ correl with Radius BMD in old men only	NT	not RF
PTH					- correl with Radius BMD in old men only		
Calcitonin	Sig lower in older men				NT	NT	NT
Conclusion	No change in bone markers with age in men cf women	Age dependant increase in OC			In old men lower radial BMD ass with high PTH. low 25OH D High OC corr to low BMD in old F & young M	urinary pyr crosslinks predict hip fracture, association appears related to disability	Bone resorption markers-CTX & free Dpyr predict hip fracture risk indepcndant of FNBMD

MORTALITY AND FACTORS INFLUENCING IT

Variables	Beals RK *J Chr Dis 72*	Jensen JS *Acta Orthop Scand 79*	Jensen JS *Injury 84*	Colbert DS *Irish J of Med Sc*	Thorngren KG *Clin Ortho & Rel Res 90*	Stavrou ZP *Acta Orthop Scand 97*	Wolinsky FD *Am J Pub Health 97*	Sernbo I *OI 93*
Study design	All hip fractures over 6 yrs 56-61 reviewed	Retrospective record reviews over 6 yrs	Consec hip fractures over 1 yr; prospective FU 3yrs	Chart reviews between 68-73	Prospective	Retrospective	Prospective study 7527 men & women aged >70yr FU 8 yrs	1429 consec fractures over 3 yrs; FU 1yr
Number of hip fractures	607	1592	518	881	103	202	368	1429
M : F	1:2.5	368:1224	101:417	252:629	28: 75	53: 149	22%M; 78%F	369, 1060
Age	all ages	>=50yrs	all ages	all ages	> 50 y; mean 75	52-95y; mean 76	>70 yrs	
Mortality period	in hosp; 1yr, 5yr, 10yr	3,6, 1y, 3y, 5y	3yr	6,12,2yr	3wk, 4M, 1, 5 and 10 yrs	1 yr	1 yr	1 yr
Mortality rate	12.5%, 50%, 84%; >90% resp	17%, 21.5%, 27%, 43% and 56% resp	35%	23%, 28% 37% resp		Overall- 18%	20% overall Presence of fracture increased risk of dying 83%	M: 34%; F: 20%
Age	RF	RF	RF			RF		RF

	Beals RK	Jensen JS	Jensen JS	Colbert DS	Thorngren KG	Stavrou ZP	Wolinsky FD	Sernbo I
Variables	*J Chr Dis 72*	*Acta Orthop Scand 79*	*Injury 84*	*Irish J of Med Sc*	*Clin Ortho & Rel Res 90*	*Acta Orthop Scand 97*	*Am J Pub Health 97*	*OI 93*
Sex		Male sex RF		Male sex RF				
Type of fracture	Subtrochanreic fracture RF	Trochanteric fracture RF						Not RF
Type/ timing of surgery	Not RF					> 3days delay in operation- RF		
Co-morbidity (Odds ratio)	CCF, Parkinsons, chronic brain syndrome RF			RF: atheroma, bed sores on admission		Cardiorespiratory diseases RF		
NH residence prior to fracture								living alone RF
Activity status prior to fracture			Pre-fracture social dependence RF					RF
History of post operative complication	Post op sepsis RF							
Conclusions	RF: age,	RF: age, male sex,	RF: age,	RF: atheroma,	Predict discharge	Age,	Fracture Vs	RF: diff with

	Beals RK	Jensen JS	Jensen JS	Colbert DS	Thorngren KG	Stavrou ZP	Wolinsky FD	Sernbo I
Variables	*J Chr Dis 72*	*Acta Orthop Scand 79*	*Injury 84*	*Irish J of Med Sc*	*Clin Ortho & Rel Res 90*	*Acta Orthop Scand 97*	*Am J Pub Health 97*	*OI 93*
	subtrochanteric fracture, comorbidity eg CCF, Parkinsons, Chr brain syndrome, post op sepsis Interval between fracture and surgery not a RF	trochanteric fracture	prefracture social dependence	bed sores on adm, male sex, concomitant illness	home 2/52-living with someone, good gen health Return home 4M-10Yr: active prefracture lifestyle; age RF for dying	type of surg (hemiarthro) and timing of surg - RF Overall higher mortality in men (data not shown)	controls: older, females, living alone, past H/o fracture, DM+, diff with ADL, limited lower body functn, H/o hospitalization 1 year prior	shopping; living alone

MORTALITY AND FACTORS INFLUENCING IT

	Magaziner J	Myers AH	Poor G	Poor G	Nettleman MD	Diamond TH	Aharonoff GB	Forsen L
Variables	*Am J Pub Health 89*	*Am J Epid 91*	*OI 95*	*Clin Ortho& Rel Res 95*	*J Gen Intern Med 96*	*MJA 97*	*J Ortho Trauma 97*	*OI 99*
Study design	Retrsopective chart reviews of all fractures over 18mths	Retrospective, medical records over 10years	Retrospective cohort-chart reviews	See OI 95 –this paper on long term outcome; controls added	Multicen, retrospective, medical notes review	Retrospec audit from medical notes of M & F in 1 yr	Consecutive 6year: Prospective FU 1yr Ambulatory, home dwelling, cognitively intact	Population based; prospective, matched pir cohort study 1825 subjects FU 9yrs
Number of hip fractures	814	27370	131		390	102	612	1825
M : F	20%(164):650	20% (5486); 21884	All Males		24 % men	51:51	20% (122); 490	487:1338
Age	>=65 yrs	> 65 yrs.	> 35; mean 79.2		Mean 82y	> 60 yrs; median 80	> 65 y	>=50yrs
Mortality period	2,6,12 M	in hospital	30 days	1, 5, 10 yr	30 days	6M, 1yr	3, 6, 12 M	9 yrs
Mortality rate	overall <40d=4.3% 3M=8.2% 6M=12.6% 1yr=17.4%	7.5-7.8% for B/Wmales cf 5.1-4.1% B/W females	16% in 30days	42, 60, 71% respectively	8.5 %	20% at 6M	6.5, 8.8 12.7% resp (men 2x fem at 1yr: 20.7% vs 10.7%	F:M 1 yr mortality 17% Vs 31%
Age	RF age >85yrs	RF-doubled q 5yr	RF; RO 1.9	RF		Not significant	RF ; > 85y	RF

	Magaziner J	Myers AH	Poor G	Poor G	Nettleman MD	Diamond TH	Aharonoff GB	Forsen L
Variables	*Am J Pub Health 89*	*Am J Epid 91*	*OI 95*	*Clin Ortho& Rel Res 95*	*J Gen Intern Med 96*	*MJA 97*	*J Ortho Trauma 97*	*OI 99*
Sex	Male sex RF	RF: OR 1.6	Male sex RF				Not RF	RF
Type of fracture		Not RF	Not RF ? few deaths				Not RF	
Type/ timing of surgery			Not RF ? few deaths				Not RF	
Post op deterioration in mental status	Delirium on admission RF		RF; RO 9.2	RF				
Dementia	Not RF		Not RF ? few deaths					
Co-morbidity (Odds ratio)	>=1 comorbid disease RF	Septicaemia RO 12.3; pneumonia 4.9; others 2X	RF	RF-dementia, CVA, COAD, CHF, MI	RF- CHF (32.3), COAD (11.1), angina (25.7)	Not sig	Not RF by themselves-but low ASA score-RF	
Activity status prior to fracture				RF		Not significant	RF	
NH residence after fracture				RF				

	Magaziner J	Myers AH	Poor G	Poor G	Nettleman MD	Diamond TH	Aharonoff GB	Forsen L
Variables	*Am J Pub Health 89*	*Am J Epid 91*	*OI 95*	*Clin Ortho& Rel Res 95*	*J Gen Intern Med 96*	*MJA 97*	*J Ortho Trauma 97*	*OI 99*
Concomitant drugs					Post-op use of aspirin – protective (OR 0.24)			
Length of hospital stay						Not significant		
H/o smoking						Not significant		
H/o alcohol						Not significant		
H/o post op complication							RF	
ASA rating							RF	
H/o Ca							RF	
Conclusions	RF age >85yrs male sex >1 comorbid disease delirium on	Double risk/5yr increase in age; males RO 1.6 of dying cf females; infectn RO 12.3	Strong impact of hip fracture on short term outcomes RF for early	Low survival explained by high co-morbidities	Post op use of aspirin significant predictor of survival	Men significantly more RF cf females. Higher	Age >85, prefracture ADL, low ASA score, post op complication - RF	

	Magaziner J	Myers AH	Poor G	Poor G	Nettleman MD	Diamond TH	Aharonoff GB	Forsen L
Variables	***Am J Pub Health 89***	***Am J Epid 91***	***OI 95***	***Clin Ortho& Rel Res 95***	***J Gen Intern Med 96***	***MJA 97***	***J Ortho Trauma 97***	***OI 99***
	admission	Race RF OR=1.1	mortality: male sex Age Presence of co-morbidity Type of surg and fracture type not RF		Comorbidities RF for fracture CCF, angina, COAD Cause of death :cardivascular diseases	mortality; sig post fracture functionl decline Age, smoking, ROH, concomittant disease, prefracture Barthel did not contribute to mortality		

OUTCOME / FACTORS ASSOCIATED WITH SURVIVAL

Variables	**Poor et al** *OI 95*	**Poor et al** *Clin Ortho& Rel Res 95*	**Nettleman MD** *J Gen Intern Med 96*	**Diamond TH** *MJA 97*	**Stavrou ZP** *Acta Orthop Scand 97*	**Aharonoff GB** *J Ortho Trauma 97*	**Myers AH** *Am J Epid 91*	**Thorngren KG** *Clin Ortho & Rel Res 90*
Study design	Retros cohort-chart reviews	See OI 95 – this paper on long term outcome; controls added	Multicen, retrospec, med notes review	Retrospec audit from med notes of M & F in 1 yr	Retros	Prospec; Ambulatory, home dwelling, cognitively intact	Retros, medical records over 10years	Prospec
No. of hip fracture	131		390	102	202	612	27, 370	103
M : F	All Men		24 %: 76%	51:51	53: 149	122: 490 ::20:80%	20:80::5486:21884	28: 75
Age	> 35; mean 79.2		Mean 82y	> 60 yrs; median 80	52-95y; mean 76	> 65 y	> 65 yrs,	> 50 y; mean 75
Mortality period	30 days	1, 5, 10 yr	30 days	6M, 1yr	1 yr	3, 6, 12M	in hospital	3wk, 4M, 1, 5, 10 yr
Mortality rate	16% in 30days	42, 60, 71% resp	8.5 %	20% at 6M	Overall-18%	6.5, 8.8 12.7% resp (men 2x fem at 1yr: 20.7% vs 10.7%	7.5-7.8% for B/Wmales cf 5.1-4.1% B/W fem	
Age	RF; RO 1.9	RF		Not significant	RF	RF ; > 85y	RF-doubled q 5yr	
Type of fracture	Not RF ? few deaths					Not RF		
Type/ timing of surgery	Not RF ? few deaths				> 3d delay in op- RF	Not RF		

Variables	Poor et al *OI 95*	Poor et al *Clin Ortho& Rel Res 95*	Nettleman MD *J Gen Intern Med 96*	Diamond TH *MJA 97*	Stavrou ZP *Acta Orthop Scand 97*	Aharonoff GB *J Ortho Trauma 97*	Myers AH *Am J Epid 91*	Thorngren KG *Clin Ortho & Rel Res 90*
Post op deterioration in mental status	RF; RO 9.2	RF						
Dementia	Not RF ? few deaths							
Co-morbidity (Odds ratio)	RF	RF-dementia, CVA, COAD, CHF, MI	RF-CHF (32.3), COAD (11.1), angina (25.7)	Not significant	Cardioresp dis RF	Not RF by themselves-but low ASA score-RF	septicaemia RO 12.3; pneumonia 4.9; others 2X	
NH residence prior to fracture	Not RF ? few deaths	RF						
Activity status prior to fracture		RF		Not significant		RF		
NH residence after fracture		RF						
Concomitant drugs			Post-op use of aspirin – protective (OR 0.24)					
Length of hosp stay				Not significant				
History of smoking				Not significant				
History of				Not				

Variables	Poor et al *OI 95*	Poor et al *Clin Ortho& Rel Res 95*	Nettleman MD *J Gen Intern Med 96*	Diamond TH *MJA 97*	Stavrou ZP *Acta Orthop Scand 97*	Aharonoff GB *J Ortho Trauma 97*	Myers AH *Am J Epid 91*	Thorngren KG *Clin Ortho & Rel Res 90*
alcohol				significant				
H/o post op complication						RF		
ASA rating						RF		
H/o Ca						RF		
Conclusions	Strong impact of hip fracture on short term outcomes	Low survival explained sp by high comorbidities	Post op use of aspirin sig predictor of survival Co-morbidities RF for fracture	men sig more RF cf females. Higher mortality; sig post fracture functionl decline	Age, type of surg (hemiarthro) and timing of surg -RF	Age >85, prefracture ADL, low ASA score, post op complicatn - RF	double risk/5yr increase in age; males RO 1.6 of dying cf females; infectn RO 12.3	Predict discharge home 2/52- living with someone, good gen health Return home 4M-10Yr: active prefracture lifestyle; age RF for dying

Appendix 2.1

HIP FRACTURES IN MEN

PATIENT IDENTIFICATION

Surname: ..... **CR No:** .....

Forename(s): ..... **Ward:** .....

Address: .....

.....

.....

Post Code: ..... **Tel No:** .....

Date of Birth: .....

Marital Status: Single/Married/Divorced/Separated/Widowed

Ethnic Origin: Caucasian/Asian/Other

Date of Interview/Scan: .....

CONDITION DURING HOSPITAL STAY

Date of fracture: ..... **Date of admission:** .....

Date of operation: .....

***Nature of operation:** .....

***Site of fracture:** Right/Left ***Type of fracture:** .....

***Any concomitant fracture (please specify):** .....

.....

SOCIODEMOGRAPHIC DATA

Education - Years in school from aged 5: ..... years

Years of higher education (after 'A' Levels): ..... years

Admitted from:

own home: ☐

another's home: ☐

residential home: ☐

nursing home/long term hospital care: ☐

hospital: ☐

other (please state): .....

Where did you live in the past?

during childhood: rural / urban

in young adulthood: rural / urban

in the recent past: rural / urban

Do you live?

alone: ☐

together with wife/children/relative: ☐

together with person/s NOT your relative: ☐

What kind of work have you done for the longest period of your life?

agriculture/farming/forestry/fishing: ☐

industrial/mining/construction/similar: ☐

office work/other white collared work: ☐

domestic work: ☐

other (please state): .....

How heavy is or was your main activity?

during childhood: sedentary / light physical / heavy physical

during young adulthood: sedentary / light physical / heavy physical

during recent past: sedentary / light physical / heavy physical

OTHER FINDINGS

Are you able to read a newspaper with or without glasses? **YES / NO**

Which glasses do you use?	distance:	☐
	reading:	☐
	bifocal:	☐
What is the colour of your skin?	light complexion:	☐
	dark complexion:	☐
	other (please specify):	.....
What was the colour of your hair (undyed) at age 20 - 30 years?	blond/fair/reddish:	☐
	brown:	☐
	black:	☐
What is the colour of your eyes?	blue/green/grey:	☐
	brown/black/mixed:	☐

Mental Score

	Correct	Slightly Wrong	False
What is your age?	☐	☐	☐
What is your name?	☐	☐	☐
What is your home address?	☐	☐	☐
What day of the week is it?	☐	☐	☐
What is the name of our prime minister?	☐	☐	☐

LIFESTYLE DATA

Physical Activity

How much time do you typically spend walking out of doors each day?

none / some, but less than half an hour / half to one hour / more than one hour

I am interested in the amount of physical activity you undertook both at work and at home at different stages of your life.

	in childhood	in adulthood	in recent past
light:	☐	☐	☐
moderate:	☐	☐	☐
heavy:	☐	☐	☐
very heavy:	☐	☐	☐

Immobilisation

Have you ever been confined to bed for a period of greater than 2 months? YES / NO

If YES, at what age? ..... years

for how long? ..... months

Smoking

Have you ever smoked? YES / NO

If YES, how old were you when you first started smoking: ..... years

How many did/do you smoke a day: .....

If you have now stopped, how old were you when you stopped: ..... years

Alcohol

On average how many units of alcohol do you drink in a week: ..... units

Have you ever drunk more regularly in the past? YES / NO

If YES, how many units per week and for how many years?

..... units per week for ..... years (average)

Caffeine How many cups of coffee do/did you usually have a day?

	in childhood	in adulthood	in recent past
never:	☐	☐	☐
sometimes:	☐	☐	☐
1 - 2 cups per day:	☐	☐	☐
3 or more cups per day:	☐	☐	☐

How many cups of tea do/did you usually have a day?

	in childhood	in adulthood	in recent past
never:	☐	☐	☐
sometimes:	☐	☐	☐
1 - 2 cups per day:	☐	☐	☐
3 or more cups per day:	☐	☐	☐

Calcium Intake

How many days in the past week did you eat each of the following milk products?

	days per week	amount
hard cheese:	.....	.....
soft cheese:	.....	.....
yoghurt:	.....	.....
milk:	.....	.....
others (ice cream):	.....	.....

For the period indicated below, mark the words that best describe how often you drank milk (include whole, low fat, skimmed).

	in childhood	in adulthood	in recent past
3 glasses or more per day:	☐	☐	☐
1 - 2 glasses per day:	☐	☐	☐
every week but not every day:	☐	☐	☐
less than once a week:	☐	☐	☐

PAST FRACTURE HISTORY

Have you ever suffered from a broken bone (fracture)? YES / NO

If YES, please state bone broken (site), age at time (years)
and cause (level of trauma) - spontaneous
- minor trauma (fall from standing height or less)
- major trauma (fall from greater than standing heigh or external injury eg. RTA/falling down stairs)

Site	Age	Cause

Have any of your parents, brothers or sisters sustained a broken bone (fracture)? YES / NO

If YES, please state bone broken (site), age at time (years) and cause (level of trauma).

Relative	Site	Age at time	Cause

Does any member of your family suffer from osteoporosis? YES / NO

If YES, please state which relative, their age at the time of diagnosis and how the diagnosis was made.

Relative	Age at time	How diagnosis was made (please delete)
		posture / loss of height / clinical examination / x-ray / BMD
		posture / loss of height / clinical examination / x-ray / BMD
		posture / loss of height / clinical examination / x-ray / BMD
		posture / loss of height / clinical examination / x-ray / BMD

CIRCUMSTANCES AROUND PRESENT FRACTURE

Site: outdoors / indoors

Time of Day: morning / midday / afternoon / evening / night

Light Conditions: in daylight / in twilight / in darkness

Physical Circumstances Around the Fall

Did the fracture follow a fall? YES / NO

If YES, was the fall:

on the same level? YES / NO

from one level to another? YES / NO

during change of posture - rising from bed? YES / NO
transferring from bed? YES / NO
transferring from chair? YES / NO
other/unknown? YES / NO

due to tripping or slipping - on a pavement? YES / NO
on the floor? YES / NO
on a rug? YES / NO
on a stairway? YES / NO
other/unknown YES / NO

in a traffic accident? YES / NO

if YES, were you: the driver/passenger of a car YES / NO
a motorcyclist? YES / NO
a cyclist? YES / NO
a pedestrian? YES / NO
other? YES / NO

any other accident? (please specify): .....

.....

Comments about cause of fracture:

ANTHROPOMETRIC DATA

Height/Length: ..... **cm**

Weight: ..... **kg**

Arm Span: ..... **cm**

***Grip Strength:** ..... **right** ..... **left**

***Body Mass Index:** ..... **weight (kg)/height (m^2)**

Hip Axis Length: ..... **cm**

LUMBAR SPINE - Measurement Reference No: _____

Site	g/cm²	T - young normals		Z - age-matched normals	
		SD	%	SD	%

FEMUR - Measurement Reference No: _____

Site	g/cm²	T - young normals		Z- - age-matched normals	
		SD	%	SD	%
Neck					
Trochanteric					
Intertrochanteric					
Ward's					

FOREARM - Measurement Reference No: _____

Site	g/cm²	T - young normals		Z - age-matched normals	
		SD	%	SD	%
Forearm					

Appendix 2.2

HIP FRACTURES IN MEN

MEDICAL QUESTIONNAIRE

FRACTURE HISTORY

Site of fracture: **Right** **Left**

Type of fracture: **Cervical** **Trochanteric**

Nature of operation: .....

Any concomitant fracture: .....

ANY CONTRIBUTING MEDICAL CONDITIONS TO FALL

Past history of falls? **YES / NO**

If YES, how frequent? .....

current stroke/paresis: ☐

cardiac disease: ☐

poor vision: ☐

dizziness: ☐

restricted mobility/Parkinson's: ☐

confused/dementia: ☐

depressed: ☐

excited: ☐

on any medications causing drowsiness: ☐

others (specify): .....

MEDICAL HISTORY

Previous diseases and medical conditions, along with operations, if any:-

blue slera: ☐

skin laxity: ☐

hypermobile: ☐

OI, Marfans, Ehler Danlos, homocystinuria: ☐

thyroid diseases - hypo/hyper: ☐

diabetes - IDDM (juvenile), NIDDM (adult): ☐

hyperparathyroidism: ☐

anorexia: ☐

milk intolerance (lactose intolerance): ☐

gastrectomy/intestinal resection: ☐

malabsorption/Crohn's/steatorrhoea/
prolonged obstructive jaundice/
chronic liver disease/cirrhosis: ☐

chronic renal disease: ☐

haemochromatosis - skin pigmentation/DM/
cardiomegaly, hepatomegaly/hypogonadal: ☐

hypogonadism: ☐

diseases needing steroids, eg nephrotic
syndrome/asthma/RA: ☐

prostate hyperplasia: ☐

DRUG HISTORY - PAST/CURRENT

Which of the following medications have you used or are currently using?

Medication	Route	Dose (min/max)	Duration	Age at start
anxiolytics				
hypnotics				
TCADs				
antipsychotics				
anticoagulants - Heparin				
antiepileptics				
thyroid preparation				
diuretics				
steroids				
antacids				
insulin				
others (specify)				

Have you taken or are you taking any of the following medications for osteoporotic bone disease?

Calcium: ☐

Vitamin D: ☐

Fluoride: ☐

Bisphosphonates

(Didronel/Alendronate): ☐

Calcitonin: ☐

Testosterone: ☐

Others (specify): .....

Appendix 2.3

HIP FRACTURES IN MEN

IMPACT

SF-36 FORM

The following questions ask you for your views about your health, how you feel and how well you are able to do your usual activities. If you are unsure about how to answer any questions, please give the best answer you can and make any of your own comments if you like.

1. In general, would you say your health is:

- Excellent ☐
- Very good ☐
- Good ☐
- Fair ☐
- Poor ☐

2. Compared to one year ago, how would you rate your general health now?

- Much better now than one year ago ☐
- Somewhat better now than one year ago ☐
- About the same ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

3. HEALTH AND DAILY ACTIVITIES

The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a)	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b)	Moderate activities, such as moving a table pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c)	Lifting or carrying groceries	☐	☐	☐
d)	Climbing several flights of stairs	☐	☐	☐
e)	Climbing one flight of stairs	☐	☐	☐
f)	Bending, kneeling or stooping	☐	☐	☐
g)	Walking more than a mile	☐	☐	☐
h)	Walking half a mile	☐	☐	☐
i)	Walking 100 yards	☐	☐	☐
j)	Bathing and dressing yourself	☐	☐	☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your <u>physical health</u>?

		Yes	No
a)	Cut down on the amount of time you spent on work or other activities	☐	☐
b)	Accomplished less than you would like	☐	☐
c)	Were limited in the kind of work or other activities	☐	☐
d)	Had difficulty performing the work or other activities (ie. it took extra effort)	☐	☐

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any <u>emotional</u> problems (such as feeling depressed or anxious)?

		Yes	No
a)	Cut down on the amount of time you spent on work or other activities	☐	☐
b)	Accomplished less than you would like	☐	☐
c)	Didn't do work or other activities as carefully as usual	☐	☐

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much bodily pain have you had during the past 4 weeks?

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

These questions are about how you feel and how things have been with you *during the past month.* (For each question, please indicate the one answer that comes closest to the way you have been feeling.)

9. How much time during the past month:

Please tick one box on each line

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a)	Did you feel full of life?	☐	☐	☐	☐	☐	☐
b)	Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c)	Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d)	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e)	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f)	Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g)	Did you feel worn out?	☐	☐	☐	☐	☐	☐
h)	Have you been a happy person?	☐	☐	☐	☐	☐	☐
i)	Did you feel tired?	☐	☐	☐	☐	☐	☐
j)	Has you health limited your social activities (like visiting friends or close relatives).	☐	☐	☐	☐	☐	☐

10. Please choose the answer that best describes how true or false each of the following statements is for you.

Please tick one box on each line

		Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
a)	I seem to get ill more easily than other people	☐	☐	☐	☐	☐
b)	I am as healthy as anybody I know	☐	☐	☐	☐	☐
c)	I expect my health to get worse	☐	☐	☐	☐	☐
d)	My health is excellent	☐	☐	☐	☐	☐

FUNCTIONAL CAPACITY *BEFORE* AND *AFTER* THIS FRACTURE

Able to dress/undress:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Able to eat:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Able to perform household chores:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Able to get up from a chair:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Able to climb stairs:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Able to wash and dry your entire body:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Can walk:	before fracture	after fracture
independently	☐	☐
with sticks/crutches	☐	☐
with Zimmer frame	☐	☐
with the help of others	☐	☐
unable to do	☐	☐

Able to walk indoors:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Able to walk outdoors:	before fracture	after fracture
without any difficulty	☐	☐
with some difficulty	☐	☐
with much difficulty	☐	☐
unable to do	☐	☐

Appendix 2.4

HIP FRACTURES IN MEN

FOLLOW UP ASSESSMENT

6 months from fracture

Surname: ..... **CR No:** .....

Forename(s): .....

Address: .....

.....

.....

Post Code: ..... **Tel No:** .....

Date of Interview/Scan: .....

Please list any fractures you have sustained since your last visit/scan.

Bone Broken	Age	Cause

Please list all medications that you are taking at present.

Name of drug	Dose	Date started	Reason for medication

Outcome of previous surgery for broken hip?

None: ☐

Wound infection: ☐

Fracture not yet healed: ☐

Further intervention required: ☐

Other (please specify if possible):

.....

.....

When you left the hospital, did you got to:

your own home: ☐

relatives or friends: ☐

long term hospital bed: ☐

nursing home: ☐

residential home: ☐

other (please specify: .....

How many times have you seen your doctor (GP) <u>for any reason</u> during the last six months? .....

Are you still being reviewed at hospital for your hip fracture? YES / NO

Do you need help with any of the following and, if so, what help do you receive?

	Friend/Relative	Social	Paid
Washing:	☐	☐	☐
Dressing:	☐	☐	☐
Cooking	☐	☐	☐
Cleaning	☐	☐	☐
Shopping:	☐	☐	☐
Walking:	☐	☐	☐

Appendix 2.5

MALE OSTEOPOROSIS STUDY

PATIENT IDENTIFICATION

Surname: ..... **CR No:** .....

Forename(s): ..... **Ward:** .....

Address: .....

.....

.....

Post Code: ..... **Tel No:** .....

Date of Birth: .....

Marital Status: Single/Married/Divorced/Separated/Widowed

Ethnic Origin: Caucasian/Asian/Other

Date of Interview/Scan: .....

SOCIODEMOGRAPHIC DATA

Education - Years in school from aged 5: ..... years

Years of higher education (after 'A' Levels): ..... years

Admitted from:

own home: ☐

another's home: ☐

residential home: ☐

nursing home/long term hospital care: ☐

hospital: ☐

other (please state): .....

Where did you live in the past?

during childhood: rural / urban

in young adulthood: rural / urban

in the recent past: rural / urban

Do you live?

alone: ☐

together with wife/children/relative: ☐

together with person/s NOT your relative: ☐

What kind of work have you done for the longest period of your life?

agriculture/farming/forestry/fishing: ☐

industrial/mining/construction/similar: ☐

office work/other white collared work: ☐

domestic work: ☐

other (please state): .....

How heavy is or was your main activity?

during childhood: sedentary / light physical / heavy physical

during young adulthood: sedentary / light physical / heavy physical

during recent past: sedentary / light physical / heavy physical

OTHER FINDINGS

Are you able to read a newspaper with or without glasses? **YES / NO**

Which glasses do you use?	distance:	☐
	reading:	☐
	bifocal:	☐

What is the colour of your skin?	light complexion:	☐
	dark complexion:	☐
	other (please specify):	.....

What was the colour of your hair (undyed) at age 20 - 30 years?	blond/fair/reddish:	☐
	brown:	☐
	black:	☐

What is the colour of your eyes?	blue/green/grey:	☐
	brown/black/mixed:	☐

Mental Score

	Correct	Slightly Wrong	False
What is your age?	☐	☐	☐
What is your name?	☐	☐	☐
What is your home address?	☐	☐	☐
What day of the week is it?	☐	☐	☐
What is the name of our prime minister?	☐	☐	☐

LIFESTYLE DATA

Physical Activity

How much time do you typically spend walking out of doors each day?

none / some, but less than half an hour / half to one hour / more than one hour

I am interested in the amount of physical activity you undertook both at work and at home at different stages of your life.

	in childhood	in adulthood	in recent past
light:	☐	☐	☐
moderate:	☐	☐	☐
heavy:	☐	☐	☐
very heavy:	☐	☐	☐

Immobilisation

Have you ever been confined to bed for a period of greater than 2 months? YES / NO

If YES, at what age? ..... years

for how long? ..... months

Smoking

Have you ever smoked? YES / NO

If YES, how old were you when you first started smoking: ..... years

How many did/do you smoke a day: .....

If you have now stopped, how old were you when you stopped: ..... years

Alcohol

On average how many units of alcohol do you drink in a week: ..... units

Have you ever drunk more regularly in the past? YES / NO

If YES, how many units per week and for how many years?

..... units per week for ..... years (average)

Caffeine How many cups of coffee do/did you usually have a day?

	in childhood	in adulthood	in recent past
never:	☐	☐	☐
sometimes:	☐	☐	☐
1 - 2 cups per day:	☐	☐	☐
3 or more cups per day:	☐	☐	☐

How many cups of tea do/did you usually have a day?

	in childhood	in adulthood	in recent past
never:	☐	☐	☐
sometimes:	☐	☐	☐
1 - 2 cups per day:	☐	☐	☐
3 or more cups per day:	☐	☐	☐

Calcium Intake

How many days in the past week did you eat each of the following milk products?

	days per week	amount
hard cheese:	.....	.....
soft cheese:	.....	.....
yoghurt:	.....	.....
milk:	.....	.....
others (ice cream):	.....	.....

For the period indicated below, mark the words that best describe how often you drank milk (include whole, low fat, skimmed).

	in childhood	in adulthood	in recent past
3 glasses or more per day:	☐	☐	☐
1 - 2 glasses per day:	☐	☐	☐
every week but not every day:	☐	☐	☐
less than once a week :	☐	☐	☐

PAST FRACTURE HISTORY

Have you ever suffered from a broken bone (fracture)? YES / NO

If YES, please state bone broken (site), age at time (years)
and cause (level of trauma) - spontaneous
- minor trauma (fall from standing height or less)
- major trauma (fall from greater than standing heigh or external injury eg. RTA/falling down stairs)

Site	Age	Cause

Have any of your parents, brothers or sisters sustained a broken bone (fracture)? YES / NO

If YES, please state bone broken (site), age at time (years) and cause (level of trauma).

Relative	Site	Age at time	Cause

Does any member of your family suffer from osteoporosis? YES / NO

If YES, please state which relative, their age at the time of diagnosis and how the diagnosis was made.

Relative	Age at time	How diagnosis was made (please delete)
		posture / loss of height / clinical examination / x-ray / BMD
		posture / loss of height / clinical examination / x-ray / BMD
		posture / loss of height / clinical examination / x-ray / BMD
		posture / loss of height / clinical examination / x-ray / BMD

CIRCUMSTANCES AROUND PRESENT FRACTURE

Site: outdoors / indoors

Time of Day: morning / midday / afternoon / evening / night

Light Conditions: in daylight / in twilight / in darkness

Physical Circumstances Around the Fall

Did the fracture follow a fall? **YES / NO**

If YES, was the fall:

on the same level? YES / NO

from one level to another? YES / NO

during change of posture - rising from bed? YES / NO
transferring from bed? YES / NO
transferring from chair? YES / NO
other/unknown? YES / NO

due to tripping or slipping - on a pavement? YES / NO
on the floor? YES / NO
on a rug? YES / NO
on a stairway? YES / NO
other/unknown YES / NO

in a traffic accident? YES / NO

if YES, were you: the driver/passenger of a car YES / NO
a motorcyclist? YES / NO
a cyclist? YES / NO
a pedestrian? YES / NO
other? YES / NO

any other accident? (please specify): .....

.....

Comments about cause of fracture:

ANTHROPOMETRIC DATA

Height/Length: ..... **cm**

Weight: ..... **kg**

Arm Span: ..... **cm**

***Grip Strength:** ..... **right** ..... **left**

***Body Mass Index:** ..... **weight (kg)/height (m^2)**

Hip Axis Length: ..... **cm**

LUMBAR SPINE - Measurement Reference No: _____

Site	g/cm²	T - young normals		Z - age-matched normals	
		SD	%	SD	%

FEMUR - Measurement Reference No: _____

Site	g/cm²	T - young normals		Z- - age-matched normals	
		SD	%	SD	%
Neck					
Trochanteric					
Intertrochanteric					
Ward's					

FOREARM - Measurement Reference No: _____

Site	g/cm²	T - young normals		Z - age-matched normals	
		SD	%	SD	%
Forearm					

Appendix 2.6

MALE OSTEOPOROSIS STUDY

6 mth - FOLLOW UP ASSESSMENT

Surname: ..... **CR No:** .....

Forename(s): ..... **GP:** .....

Address: .....

.....

.....

Post Code: ..... **Tel No:** .....

Date of Interview/Scan: .....

Please list any fractures you have sustained since your last visit/scan.

Bone Broken	Age	Cause

Please list all medications that you are taking at present.

Name of drug	Dose	Date started	Reason for medication

Where are you now living?

in your own home: ☐

with relatives or friends: ☐

in a long term hospital bed: ☐

in a nursing home: ☐

in a residential home: ☐

other (please specify: .....

How many times have you seen your doctor (GP) for any reason during the last six months? .....

Are you being reviewed in hospital for any medical condition? YES / NO

Do you need help with any of the following and, if so, what help do you receive?

	Friend/Relative	Social	Paid
Washing:	☐	☐	☐
Dressing:	☐	☐	☐
Cooking	☐	☐	☐
Cleaning	☐	☐	☐
Shopping:	☐	☐	☐
Walking:	☐	☐	☐

Appendix 2.7

HIP FRACTURES IN MEN

FOLLOW UP ASSESSMENT

12 months from fracture

Surname: ..... **CR No:** .....

Forename(s): .....

Address: .....

.....

.....

Post Code: ..... **Tel No:** .....

Date of Interview/Scan: .....

Please list any fractures you have sustained since your last visit/scan.

Bone Broken	Age	Cause

Please list all medications that you are taking at present.

Name of drug	Dose	Date started	Reason for medication

Where are you now living?

in your own home: ☐

with relatives or friends: ☐

in a long term hospital bed: ☐

in a nursing home: ☐

in a residential home: ☐

other (please specify: .....

How many times have you seen your doctor (GP) <u>for any reason</u> during the last six months? .....

Are you still being reviewed at hospital for your hip fracture? YES / NO

Do you need help with any of the following and, if so, what help do you receive?

	Friend/Relative	Social	Paid
Washing:	☐	☐	☐
Dressing:	☐	☐	☐
Cooking	☐	☐	☐
Cleaning	☐	☐	☐
Shopping:	☐	☐	☐
Walking:	☐	☐	☐

Appendix 2.8

MALE OSTEOPOROSIS STUDY

12 mth - FOLLOW UP ASSESSMENT

Surname: ..... **CR No:** .....

Forename(s): ..... **GP:** .....

Address: .....

.....

.....

Post Code: ..... **Tel No:** .....

Date of Interview/Scan: .....

Please list any fractures you have sustained since your last visit/scan.

Bone Broken	Age	Cause

Please list all medications that you are taking at present.

Name of drug	Dose	Date started	Reason for medication

Where are you now living?

in your own home: ☐

with relatives or friends: ☐

in a long term hospital bed: ☐

in a nursing home: ☐

in a residential home: ☐

other (please specify: .....

How many times have you seen your doctor (GP) <u>for any reason</u> during the last six months? .....

Are you being reviewed at hospital for any medical condition? YES/NO

Do you need help with any of the following and, if so, what help do you receive?

	Friend/Relative	Social	Paid
Washing:	☐	☐	☐
Dressing:	☐	☐	☐
Cooking	☐	☐	☐
Cleaning	☐	☐	☐
Shopping:	☐	☐	☐
Walking:	☐	☐	☐

Appendix 2.9

HIP FRACTURES IN MEN

FOLLOW UP ASSESSMENT

24 months from fracture

Demographic data: **Tel No:** .....

Date : .....

Please list any fractures you have sustained since your hip fracture/ in the last 2years.

Bone Broken	Age	Date/ year	Cause

Where are you now living?

in your own home: ☐

with relatives or friends: ☐

in a long term hospital bed: ☐

in a nursing home: ☐

in a residential home: ☐

other (please specify: .....

Do you need help with any of the following and, if so, what help do you receive?

	Friend/Relative	Social	Paid
Washing:	☐	☐	☐
Dressing:	☐	☐	☐
Cooking	☐	☐	☐
Cleaning	☐	☐	☐
Shopping:	☐	☐	☐
Walking:	☐	☐	☐

Have you had any falls in the last year? Yes No

If yes, how many? .....

Appendix 2.10

MALE OSTEOPOROSIS STUDY

24 mth - FOLLOW UP ASSESSMENT

Demographic data:

Tel No: .....

Date : .....

Please list any fractures you have sustained since your last scan / in the previous 2 years.

Bone Broken	Age	Date/ Year	Cause

Where are you now living?

in your own home: ☐

with relatives or friends: ☐

in a long term hospital bed: ☐

in a nursing home: ☐

in a residential home: ☐

other (please specify: .....

Do you need help with any of the following and, if so, what help do you receive?

	Friend/Relative	Social	Paid
Washing:	☐	☐	☐
Dressing:	☐	☐	☐
Cooking	☐	☐	☐
Cleaning	☐	☐	☐
Shopping:	☐	☐	☐
Walking:	☐	☐	☐

Have you had any falls in the last year? Yes No

If yes, how many? .....

Appendix 3

SF 36 IN CASES AND CONTROLS

Pre-fracture quality of life assessed by SF-36 in cases and controls

Domain	Cases		Controls		Significance
	Number	*Median (IQ range)*	*Number*	*Median (IQ range)*	*Mann-Whitney U test*
Energy and Vitality	81	60 (38-73)	100	70 (55-80)	<0.01
Physical function	83	40 (10-80)	100	85 (45-90)	<0.01
Physical Role Limitation	83	50 (0-100)	100	100 (50-100)	<0.01
Social function	85	78 (33-100)	100	100 (89-100)	<0.01
Mental Health	81	76 (60-92)	100	88 (80-92)	<0.01
Mental Role Limitation	83	100 (0-100)	100	100 (100-100)	<0.01
Health Perception	81	60 (40-80)	100	70 (65-90)	<0.01
Pain	81	89 (56-100)	100	83 (67-100)	NS

Quality of life over 24 months assessed by SF-36 in cases and controls (median and interquartile ranges)

Domain	Time	Cases		Controls		Difference between groups
		Numb	*Median (IQ range)*	*Numb*	*Median (IQ range)*	*Mann-Whitney U test*
Energy	*0*	81	60 (38-73)	100	70 (55-80)	<0.01
	6	51	55 (35-75)	97	65 (50-80)	<0.01
	12	47	45 (35-60)	87	65 (50-80)	<0.01
	24	34	43 (30-51)	84	65 (46-80)	<0.01
Pain	*0*	81	89 (56-100)	100	83 (67-100)	NS
	6	51	89 (44-100)	97	78 (50-100)	NS
	12	47	78 (33-100)	87	89 (67-100)	NS
	24	34	56 (44-81)	84	78 (56-100)	<0.01
Physical function	*0*	83	40 (10-80)	100	85 (45-90)	<0.01
	6	51	20 (0-40)	97	75 (35-90)	<0.01
	12	47	15 (0-45)	87	75 (45-90)	<0.01
	24	34	20 (5-55)	84	73 (38-90)	<0.01
Social function	*0*	85	78 (33-100)	100	100 (89-100)	<0.01
	6	51	56 (11-89)	97	100 (72-100)	<0.01
	12	47	56 (22-100)	87	100 (67-100)	<0.01
	24	34	56 (22-78)	84	94 (56-100)	<0.01

Functional status at first visit in cases and controls

Activities of daily living		No.	Without difficulty	With some difficulty	With much difficulty	Unable to do	$\chi 2$
Able to dress/undress	*Cases*	**91**	58.2	16.5	15.4	9.9	$\chi 2=22.2$, df=3
	Controls	**100**	84	13	1	2	p<0.000
Able to eat	*Cases*	**91**	81.3	12.1	4.4	2.2	$\chi 2=11.7$, df=3
	Controls	**100**	96	4	0	0	p<0.008
Able to perform household chores	*Cases*	**91**	33	29.7	7.7	29.7	$\chi 2=37.6$, df=3
	Controls	**100**	76	15	2	7	p<0.000
Able to get up from a chair	*Cases*	**91**	50.5	33	14.3	2.2	$\chi 2=20.4$, df=3
	Controls	**100**	77	19	1	3	p<0.000
Able to climb stairs	*Cases*	**91**	39.6	27.5	13.2	19.8	$\chi 2=16.1$, df=3
	Controls	**100**	64	24	7	5	p<0.000
Able to wash & dry their body	*Cases*	**91**	54.9	18.7	7.7	18.7	$\chi 2=24.6$, df=3
	Controls	**100**	85	11	2	2	p<0.000
Able to walk indoors	*Cases*	**91**	59.3	26.4	9.9	4.4	$\chi 2=22.1$, df=3
	Controls	**100**	87	12	0	1	p<0.000
Able to walk outdoors	*Cases*	**91**	46.2	26.4	11	16.5	$\chi 2=24.9$, df=3
	Controls	**100**	80	13	3	4	p<0.000

Functional status at 6 months in cases and controls

Activities of daily living		No.	Without difficulty	With some difficulty	With much difficulty	Unable to do	$\chi 2$
Able to dress/undress	*Cases*	**50**	34	34	12	20	$\chi 2=27.9$, df=3
	Controls	**98**	75.5	18.4	3.1	3.1	p<0.000
Able to eat	*Cases*	**50**	74	20	4	2	$\chi 2=16.6$, df=3
	Controls	**98**	95.9	4.1	0	0	p<0.001
Able to perform household chores	*Cases*	**50**	14	26	10	50	$\chi 2=44.7$, df=3
	Controls	**98**	66.3	15.3	9.2	9.2	p <0.000
Able to get up from a chair	*Cases*	**50**	44	32	6	18	$\chi 2=14.4$, df=3
	Controls	**98**	70.4	21.4	5.1	3.1	p <0.002
Able to climb stairs	*Cases*	**50**	18	40	2	40	$\chi 2=40.9$, df=3
	Controls	**98**	63.3	20.4	9.2	7.1	p <0.000
Able to wash & dry their body	*Cases*	**50**	40	24	6	30	$\chi 2=23.1$, df=3
	Controls	**98**	74.5	17.3	3.1	5.1	p <0.000
Able to walk indoors	*Cases*	**50**	32	40	10	18	$\chi 2=33.2$, df=3
	Controls	**98**	78.6	15.3	4.1	2	p <0.000
Able to walk outdoors	*Cases*	**50**	24	36	18	22	$\chi 2=28.1$, df=3
	Controls	**98**	67	22.7	5.2	5.2	p <0.000

Functional status at 1 year in cases and controls

Activities of daily living		No.	Without difficulty	With some difficulty	With much difficulty	Unable to do	$\chi 2$
Able to dress/undress	*Cases*	47	36.2	31.9	6.4	25.5	$\chi 2$=27.4, df=3
	Controls	87	77	17.2	3.4	2.3	p <0.000
Able to eat	*Cases*	47	83	8.5	8.5	0	$\chi 2$=6.1, df=3
	Controls	87	93.1	4.6	1.1	1.1	NS
Able to perform household chores	*Cases*	47	19.1	21.3	14.9	44.7	$\chi 2$=36.6, df=3
	Controls	87	62.1	25.3	5.7	6.9	p <0.000
Able to get up from a chair	*Cases*	47	36.2	44.7	8.5	10.6	$\chi 2$=14.7, df=3
	Controls	87	66.7	27.6	4.6	1.1	p <0.002
Able to climb stairs	*Cases*	47	14.9	38.3	17	29.8	$\chi 2$=32.4, df=3
	Controls	87	58.6	27.6	10.3	3.4	p <0.000
Able to wash & dry their body	*Cases*	47	38.3	29.8	0	31.9	$\chi 2$=27.9, df=3
	Controls	87	77	18.4	1.1	3.4	p <0.000
Able to walk indoors	*Cases*	47	36.2	38.3	10.6	14.9	$\chi 2$=34.3, df=3
	Controls	87	83.9	13.8	1.1	1.1	p <0.000
Able to walk outdoors	*Cases*	47	23.4	44.7	8.5	23.4	$\chi 2$=34.8, df=3
	Controls	87	69	20.7	9.2	1.1	p <0.000

Functional status at 2 years in cases and controls

Activities of daily living			Without difficulty	With some difficulty	With much difficulty	Unable to do	$\chi 2$
Able to dress/undress	*Cases*	35	31.4	37.1	11.4	20	$\chi 2$=25.5, df=3
	Controls	84	75	19	4.8	1.2	p <0.000
Able to eat	*Cases*	35	77.1	20	0	2.9	$\chi 2$=7.4, df=3
	Controls	84	94	4.8	0	1.2	p <0.03
Able to perform household chores	*Cases*	35	20	34.3	11.4	34.3	$\chi 2$=30.7, df=3
	Controls	84	71.4	14.3	8.3	6	p <0.000
Able to get up from a chair	*Cases*	35	25.7	40	20	14.3	$\chi 2$=24.8, df=3
	Controls	84	61.9	33.3	4.8	0	p <0.000
Able to climb stairs	*Cases*	35	20	31.4	11.4	37.1	$\chi 2$=21.5, df=3
	Controls	84	56	29.8	7.1	7.1	p <0.000
Able to wash & dry their body	*Cases*	35	31.4	28.6	8.6	31.4	$\chi 2$=27.1, df=3
	Controls	84	71.4	17.9	8.3	2.4	p <0.000
Able to walk indoors	*Cases*	35	34.3	40	5.7	20	$\chi 2$=35.7, df=3
	Controls	84	84.5	11.9	3.6	0	p <0.000
Able to walk outdoors	*Cases*	35	25.7	31.4	11.4	31.4	$\chi 2$=24.0, df=3
	Controls	84	67.9	17.9	9.5	4.8	p <0.000

Functional capacity (mean HAQ scores) in cases and controls

		Baseline	6 months	12 months	24 months	Paired t test*
HAQ score	Cases	0.83	1.2	1.2	1.2	<0.001
	Controls	0.27	0.40	0.36	0.39	<0.001

* Paired t test p<0.001 between baseline-6months, 6-12 months and 12-24 months
Cases versus controls: t test at baseline, 6, 12 and 24 months p<0.001

Social impact at 6 months

			No help	Relative	Social	Paid	$\chi 2$
Help with washing	*Cases*	**52**	32.7	17.3	3.8	46.2	$\chi 2$=50.24, df=3
	Controls	**98**	87.8	6.1	0	6.1	p <0.000
Help with cooking	*Cases*	**52**	17.3	34.6	1.9	46.2	$\chi 2$=61.3, df=3
	Controls	98	82.7	9.2	0	8.2	p <0.000
Help with cleaning	*Cases*	**52**	11.5	25	3.8	59.6	$\chi 2$=60.1, df=3
	Controls	**98**	76.5	10.2	0	13.3	p <0.000
Help with shopping	*Cases*	**52**	17.3	32.7	3.8	46.2	$\chi 2$=56.5, df=3
	Controls	**98**	79.6	11.2	2	7.1	p <0.000

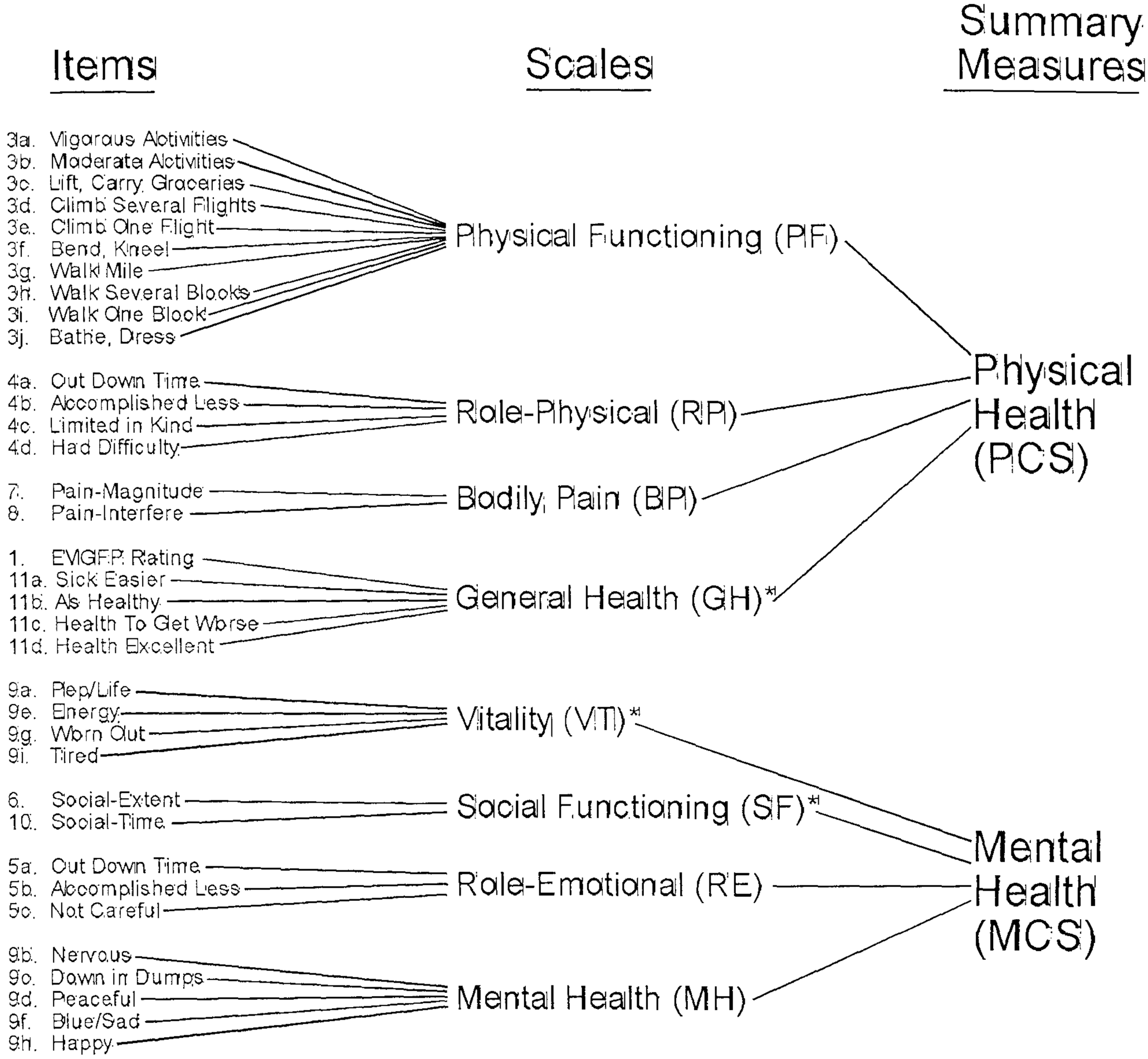
Social impact at 12 months

		No help	Relative	Social	Paid	$\chi 2$
Help with washing	*Cases*	48.3	24.1	6.9	20.7	$\chi 2$=25.02, df=3
	Controls	90.7	3.5	2.3	3.5	p <0.000
Help with cooking	*Cases*	17.2	41.4	10.3	31	$\chi 2$=56.7, df=3
	Controls	89.5	5.8	0	4.7	p <0.000
Help with cleaning	*Cases*	17.2	37.9	10.3	34.5	$\chi 2$=46.9, df=3
	Controls	83.7	5.8	0	10.5	p <0.000
Help with shopping	*Cases*	27.6	37.9	10.3	24.1	$\chi 2$=45.6, df=3
	Controls	89.5	4.7	0		p <0.000

Social impact at 24 months

		No help	Relative	Social	Paid	$\chi 2$
Help with washing	*Cases*	51.4	25.7	0	22.9	$\chi 2$=23.4, df=3
	Controls	89.4	5.9	1.2	3.5	p <0.000
Help with cooking	*Cases*	37.1	37.1	0	25.7	$\chi 2$=24.8, df=3
	Controls	81.2	12.9	1.2	4.7	p <0.000
Help with cleaning	*Cases*	31.4	37.1	2.9	28.6	$\chi 2$=23.1, df=3
	Controls	77.6	11.8	1.2	9.4	p <0.000
Help with shopping	*Cases*	28.6	42.9	0	28.6	$\chi 2$=30.9, df=3
	Controls	80	12.9	1.2	5.9	p <0.000

FIGURE 1 SF-36 MEASUREMENT MODEL



* Significant correlation with other summary measure.

Source: Ware et al. (1994)

Table 1: Summary of Information About SF-36 Scales and Physical and Mental Component Summary Measures

Scales	Correlations		Number of		Mean	SD	Reli-ability	CI[a]	Definition (% observed)	
	PCS	MCS	Items	Levels					Lowest Possible Score (Floor)[c]	Highest Possible Score(Ceiling)[c]
Physical Functioning (PF)	.85	.12	10	21	84.2	23.3	.93	12.3	Very limited in performing all physical activities including bathing or dressing (0.8%)	Performs all types of physical activities including the most vigorous without limitations due to health (38.8%)
Role- Physical (RP)	.81	.27	4	5	80.9	34.0	.89	22.6	Problems with work or other daily activities as a result of physical health (10.3%)	No problems with work or other daily activities (70.9%)
Bodily Pain (BP)	.76	.28	2	11	75.2	23.7	.90	15.0	Very severe and extremely limiting pain (0.6%)	No pain or limitations due to pain (31.9%)
General Health (GH)	.69	.37	5	21	71.9	20.3	.81	17.6	Evaluates personal health as poor and believes it is likely to get worse (0.0%)	Evaluates personal health as excellent (7.4%)
Vitality (VT)	.47	.65	4	21	60.9	20.9	.86	15.6	Feels tired and worn out all of the time (0.5%)	Feels full of pep and energy all of the time (1.5%)
Social Functioning (SF)	.42	.67	2	9	83.3	22.7	.68	25.7	Extreme and frequent interference with normal social activities due to physical and emotional problems (0.6%)	Performs normal social activities without interference due to physical or emotional problems (52.3%)
Role-Emotional (RE)	.16	.78	3	4	81.3	33.0	.82	28.0	Problems with work or other daily activities as a result of emotional problems (9.6%)	No problems with work or other daily activities (71.0%)
Mental Health (MH)	.17	.87	5	26	74.7	18.1	.84	14.0	Feelings of nervousness and depression all of the time (0.0%)	Feels peaceful, happy, and calm all of the time (0.2%)
Physical Component Summary (PCS)			35	567[b]	50.0	10.0	.92	5.7	Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated "poor" (0.0%)	No physical limitations, disabilities, or decrements in well-being, high energy level, health rated "excellent" (0.0%)
Mental Component Summary (MCS)			35	493[b]	50.0	10.0	.88	6.3	Frequent psychological distress, social and role disability due to emotional problems, health rated "poor" (0.0%)	Frequent positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent" (0.0%)

SUMMINFO.TAB

[a] CI = 95% confidence interval.
[b] Number of levels observed at baseline; scores rounded to the first decimal place (n = 2,474).
[c] Percentage observed comes from general U.S. population sample.
Source: Ware, Kosinski, and Keller, 1994.